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L4 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2002 ACS
2002:157948 Document No. 136:205503 Tissue engineering **scaffolds** promoting matrix protein production. West, Jennifer L.; Mann, Brenda K. (Rice University, USA). PCT Int. Appl. WO 2002016557 A2 20020228, 25 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO

2001-US26170 20010821. PRIORITY: US 2000-PV226771 20000821.

AB Matrix-enhancing mols., such as **TGF-.beta.**, are conjugated to or immobilized on **scaffolds** to increase ECM prodn. by cells for tissue engineering, tissue regeneration and wound healing applications. The matrix-enhancing mol. is conjugated to a tether, such as polyethylene glycol (PEG) monoacrylate, for attachment to a tissue engineering or cell growth **scaffold**. The matrix-enhancing mol. retains activity after attachment to the **scaffold**, and causes cells growing in or on the **scaffold** to increase **extracellular matrix** (ECM) prodn., without substantially increasing proliferation of the cells, even when the **scaffold** addnl. contains cell adhesion ligands. The increased ECM produced by the cells aids in maintaining the integrity of the **scaffold**, particularly when the **scaffold** is degradable, either by hydrolysis or by enzymic degrdn. For example, TNF.beta. was conjugated to polyethylene glycol by reacting TNF.beta. with acryloyl-PEG-N-hydroxysuccinimide in TRIS buffer (pH 8.5) for 2 h. The mixt. was then lyophilized and stored frozen. Smooth muscle cells were cultured in presence of 0.04 pmol/mL acryloyl-PEG-**TGF.beta**. and prodn. of **extracellular matrix** protein was evaluated.

L4 ANSWER 2 OF 19 MEDLINE DUPLICATE 1

2002400945 Document Number: 22128914. PubMed ID: 12021267.

Context-specific effects of fibulin-5 (DANCE/EVEC) on cell proliferation, motility, and invasion. Fibulin-5 is induced by transforming growth factor-beta and affects protein kinase cascades. Schiemann William P; Blobe Gerard C; Kalume Dario E; Pandey Akhilesh; Lodish Harvey F. (Whitehead Institute for Biomedical Research, Cambridge, MA 02142, USA.. schiemannwp@njc.org) . JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jul 26) 277 (30) 27367-77. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Fibulin-5 (FBLN-5; also known as DANCE or EVEC) is an integrin-binding **extracellular matrix** protein that mediates endothelial cell adhesion; it is also a calcium-dependent elastin-binding protein that **scaffolds** cells to elastic fibers, thereby preventing elastinopathy in the skin, lung, and vasculature. Transforming growth factor-beta (**TGF-beta**) regulates the production of cytokines, growth factors, and **extracellular matrix** proteins by a variety of cell types and tissues. We show here that **TGF-beta** stimulates murine 3T3-L1 fibroblasts to synthesize FBLN-5 transcript and protein through a Smad3-independent pathway. Overexpression of FBLN-5 in 3T3-L1 cells increased DNA synthesis and enhanced basal and **TGF-beta**-stimulated activation of ERK1/ERK2 and p38 mitogen-activated protein kinase (MAPK). FBLN-5 overexpression also augmented the tumorigenicity of human HT1080 fibrosarcoma cells by increasing their DNA synthesis, migration toward fibronectin, and invasion through synthetic basement membranes. In stark contrast, FBLN-5 expression was down-regulated in the majority of metastatic human malignancies, particularly in cancers of the kidney, breast, ovary, and colon. Unlike its proliferative response in fibroblasts, FBLN-5 overexpression in mink lung Mv1Lu epithelial cells resulted in an antiproliferative response, reducing their DNA synthesis and cyclin A expression. Moreover, FBLN-5 synergizes with **TGF-beta** in stimulating AP-1 activity in Mv1Lu cells, an effect that was abrogated by overexpression of dominant-negative versions of either MKK1 or p38 MAPKalpha. Accordingly, both the stimulation and duration of ERK1/ERK2 and p38 MAPK by **TGF-beta** was enhanced in Mv1Lu cells expressing FBLN-5. Our findings identify FBLN-5 as a novel **TGF-beta**-inducible target gene that regulates cell growth and motility in a context-specific manner and affects protein kinase activation by **TGF-beta**. Our findings also indicate that aberrant FBLN-5 expression likely contributes to tumor development in humans.

L4 ANSWER 3 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002322103 EMBASE Interaction of chondrocytes, **extracellular matrix** and growth factors: Relevance for articular cartilage tissue engineering. van der Kraan P.M.; Buma P.; van Kuppevelt T.; van den Berg W.B.. P.M. van der Kraan, Lab. for Experimental Rheumatology, Nijmegen Ctr. for Mol. Life Sciences, University Medical Centre Nijmegen, Geert Grooteplein 26-28, Nijmegen, Netherlands. p.vanderkraan@ncmls.nl. Osteoarthritis and Cartilage 10/8 (631-637) 2002.
Refs: 82.
ISSN: 1063-4584. CODEN: OSCAEO. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The abundant **extracellular matrix** of articular cartilage has to be mantained by a limited number of chondrocytes. Vice versa, the **extracellular matrix** has an important role in the regulation of chondrocyte function. Objective: In this review we discuss the role of the **extracellular matrix** in the regulation of chondrocyte function and the relevance for cartilage tissue engineering. To reach this goal the international literature on this subject has been searched with a major focus on the last 5 years. Results: Structural matrix macromolecules (eg. collagen, hyaluronate), but also growth factors (e.g. IGF-I, **TGF .beta.**) entrapped in the matrix and released under specific conditions affect chondrocyte behavior. These factors communicate with the chondrocyte via specific membrane receptors. In this way there is a close interaction between the extracellular and intracellular Milleu. Articular cartilage has a limited capacity of intrinsic repair which has resulted in the development of tissue engineering approaches to repair damaged cartilage. Successful application of **scaffolds** has to take into account the important role of both soluble and insoluble matrix-derived factors in cartilage homeostasis. Conclusion: Functional tissue engineering will only be realized when the **scaffolds** used will provide cartilage cells with the correct extracellular signals. .COPYRGT. 2002 Published by Elsevier Science Ltd on behalf of OsteoArthritis Research Society International.

L4 ANSWER 4 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
2002246893 EMBASE In vivo mesenchymal cell recruitment by a **scaffold** loaded with transforming growth factor .beta.1 and the potential for in situ chondrogenesis. Huang Q.; Goh J.C.H.; Hutmacher D.W.; Lee E.H.. Dr. E.H. Lee, Department of Orthopedic Surgery, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260, Singapore. meddean@nus.ed.sg. Tissue Engineering 8/3 (469-482) 2002.
Refs: 44.
ISSN: 1076-3279. CODEN: TIENFP. Pub. Country: United States. Language: English. Summary Language: English.

AB The objectives of this study were (1) to develop a biphasic implant made of a bioresorbable polymeric **scaffold** in combination with **TGF-.beta.**1-loaded fibrin glue for tissue-engineering applications, and (2) to determine whether the implant made of a polycaprolactone (PCL) **scaffold** and **TGF-.beta** .1-loaded fibrin glue could recruit mesenchymal cells and induce the process of cartilage formation when implanted in ectopic sites. Twenty-four 6-month-old New Zealand White rabbits were used. **Scaffolds** loaded with various doses of **TGF-.beta** .1 in fibrin glue were implanted subcutaneously, intramuscularly, and subperiosteally. The rabbits were killed and implants were removed at 2, 4, and 6 weeks postoperatively. The specimens were subjected to various staining techniques for histological analysis. Light microscopic examination of all specimens revealed that the entire pore space of the **scaffolds** was filled with various tissues in each group. The entire volume of the **scaffolds** in the groups loaded with **TGF-.beta.**1 and implanted intramuscularly and

subcutaneously was populated with mesenchymal cells surrounded with an abundant **extracellular matrix** and blood vessels. The **scaffold** loaded with **TGF-.beta.**1 and implanted subperiosteally was found to be richly populated with chondrocytes at 2 and 4 weeks and immature bone formation was identified at 6 weeks. We conclude that **scaffolds** loaded with **TGF-.beta** .1 can successfully recruit mesenchymal cells and that chondrogenesis occurred when this construct was implanted subperiosteally.

L4 ANSWER 5 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 3
2002158789 EMBASE Molecular tissue engineering: Applications for articular repairing using cultured allogeneic mesenchymal stem cells transduced with the transforming growth factor .beta.(1) gene. Guo X.-D.; Du J.-Y.; Zheng Q.-X.; Liu Y.; Duan D.-Y.; Quan D.-P.; Lu Z.-J.. X.-D. Guo, Department of Orthopaedics, Tongji Medical College, Huazhong Univ. of Science/Technology, Wuhan 430022, China. Chinese Journal of Biomedical Engineering 21/2 (111-117+131) 2002.
Refs: 20.
ISSN: 0258-8021. CODEN: ZSYXEI. Pub. Country: China. Language: Chinese. Summary Language: English; Chinese.

AB Objective: Transforming growth factor beta (**TGF-.beta** .(1)) is a multifunctional molecule that plays a central role in promotion of cartilage repair and inhibition of inflammatory and alloreactive immune response. Cell mediated gene therapy can allow a sustained expression of the **TGF-.beta.**(1) that may circumvent difficulties associated with growth factor delivery. The objective of this experimental study was to investigate whether the **TGF-.beta.**(1) gene modified mesenchymal stem cells (MSCs) could enhance the repair of full-thickness articular cartilage defects in allogeneic rabbits. Methods: The **TGF-.beta.**(1) gene transduced periosteum-derived MSCs were seeded into biodegradable poly-DL-lactide (PDLLA) three-dimensional porous **scaffolds** coated with poly-L-lysine and allografted into full-thickness articular cartilage defect in 18 New Zealand White rabbits. The follow-up times were 2,4,12 and 24 weeks. Histological, ultrastructural and immunohistological studies were done. Results: In vivo, cartilaginous repair tissue were observed after implantation of **scaffolds** seeded with transduced MSCs, 24 weeks-repair was histologically and ultrastructurally better for pcDNA(3)-**TGF-.beta.**(1) gene modified MSCs/**scaffolds** composites than for pcDNA(3) gene alone control groups, with respect to: (I) Synthesis of hyaline cartilage specific **extracellular matrix** (e.g. type II collagen); (II) reconstitution of the underlying bone; (III) inhibition of inflammatory and allorective immune response. Conclusion: The **TGF-.beta.**(1) gene transduced MSCs/poly-L-lysine coated PDLLA composite allografts used in this study was the first attempt to combine the principles of tissue engineering with principles of molecular biology organically for articular cartilage repair. This new molecular tissue engineering approach could be of potential benefit to enhance the repair of damaged articular cartilage, especially those caused by osteoarthritis. A novel concept, molecular tissue engineering, was put forward for the first time. As a rising branch, it represents both a new domain and a significant trend of tissue engineering research.

L4 ANSWER 6 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002088303 EMBASE Differential effects of growth factors on tissue-engineered cartilage. Blunk T.; Sieminski A.L.; Gooch K.J.; Courter D.L.; Hollander A.P.; Nahir A.M.; Langer R.; Vunjak-Novakovic G.; Freed L.E.. Dr. L.E. Freed, Massachusetts Inst. of Technology, Building E25, 77 Massachusetts Ave., Cambridge, MA 02139, United States. Lfreed@mit.edu. Tissue Engineering 8/1 (73-84) 2002.
Refs: 42.
ISSN: 1076-3279. CODEN: TIENFP. Pub. Country: United States. Language:

English. Summary Language: English.

AB The effects of four regulatory factors on tissue-engineered cartilage were examined with specific focus on the ability to increase construct growth rate and concentrations of glycosaminoglycans (GAG) and collagen, the major **extracellular matrix** (ECM) components. Bovine calf articular chondrocytes were seeded onto biodegradable polyglycolic acid (PGA) **scaffolds** and cultured in medium with or without supplemental insulin-like growth factor (IGF-I), interleukin-4 (IL-4), transforming growth factor-.beta.1 (**TGF-.beta.**1) or platelet-derived growth factor (PDGF). IGF-I, IL-4, and **TGF-.beta.**1 increased construct wet weights by 1.5-2.9-fold over 4 weeks of culture and increased amounts of cartilaginous ECM components. IGF-I (10-300 ng/mL) maintained wet weight fractions of GAG in constructs seeded at high cell density and increased by up to fivefold GAG fractions in constructs seeded at lower cell density. **TGF-.beta**.1 (30 ng/mL) increased wet weight fractions of total collagen by up to 1.4-fold while maintaining a high fraction of type II collagen (79 .+-. 11% of the total collagen). IL-4 (1-100 ng/mL) minimized the thickness of the GAG-depleted region at the construct surfaces. PDGF (1-100 ng/mL) decreased construct growth rate and ECM fractions. Different regulatory factors thus elicit significantly different chondrogenic responses and can be used to selectively control the growth rate and improve the composition of engineered cartilage.

L4 ANSWER 7 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4

2002001005 EMBASE **TGF-.beta.**1 up-regulates paxillin protein expression in malignant astrocytoma cells: Requirement for a fibronectin substrate. Han X.; Stewart J.E. Jr.; Bellis S.L.; Benveniste E.N.; Ding Q.; Tachibana K.; Grammer J.R.; Gladson C.L.. C.L. Gladson, University of Alabama, LHRB 567, 701 S. 19th Street, Birmingham, AL 35294, United States. Gladson@path.uab.edu. Oncogene 20/55 (7976-7986) 29 Nov 2001.

Refs: 20.

ISSN: 0950-9232. CODEN: ONCNES. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Cytokines can influence the interactions between members of the integrin cell adhesion receptor family and the **extracellular matrix** thereby potentially affecting cell function and promoting cell adhesion, growth and migration of malignant astrocytoma tumor cells. As malignant astrocytoma cells synthesize **TGF-.beta.**1 in vivo, we analysed the effects of **TGF-.beta.**1 on signaling events associated with integrin receptor ligation, focusing on the effects on paxillin, a phosphorylated adaptor protein, that acts as a **scaffold** for signaling molecules recruited to focal adhesions. **TGF-.beta.**1-stimulation of primary astrocytes and serum-starved U-251MG malignant astrocytoma cells attached to fibronectin induced a substantial increase in the levels of paxillin protein (fivefold increase at 2.0 ng/ml) in a dose- and time-dependent manner compared to the levels observed on plating onto fibronectin in the absence of stimulation. In the astrocytoma cells, this resulted in an increase in the pool of tyrosine-phosphorylated paxillin, although it did not appear to alter the extent of phosphorylation of the paxillin molecules. In contrast, in primary astrocytes the protein levels were upregulated in the absence of a parallel increase in phosphorylation. The **TGF-.beta.**1-stimulated increase in paxillin levels required ligation of the fibronectin receptor, as it was not induced when the cells were plated onto vitronectin, collagen or laminin. The increase in the pool of paxillin on **TGF-.beta.**1 stimulation of the fibronectin-plated astrocytoma cells was associated with an increase in translation, but was not associated with an increase in the steady-state levels of paxillin mRNA. Stimulation with **TGF-.beta.**1 on a fibronectin substrate increased subsequent attachment and spreading of U-251MG cells onto fibronectin and, to a lesser extent, vitronectin,

but not collagen. Our results indicate that physiologic levels of **TGF-.beta.1** stimulate the expression of paxillin protein at the level of translation through a process that requires engagement of the fibronectin receptor, and promotes attachment and spreading of malignant astrocytoma cells on fibronectin.

L4 ANSWER 8 OF 19 MEDLINE DUPLICATE 5
2001668772 Document Number: 21571363. PubMed ID: 11714656. Adenovirus-mediated gene transfer of a secreted transforming growth factor-beta type II receptor inhibits luminal loss and constrictive remodeling after coronary angioplasty and enhances adventitial collagen deposition. Kingston P A; Sinha S; David A; Castro M G; Lowenstein P R; Heagerty A M. (Molecular Medicine and Gene Therapy Unit, University of Manchester, Department of Medicine, Manchester Royal Infirmary, Manchester, UK.) CIRCULATION, (2001 Nov 20) 104 (21) 2595-601. Journal code: 0147763. ISSN: 1524-4539. Pub. country: United States. Language: English.

AB BACKGROUND: **Extracellular matrix** (ECM) remodeling is central to the development of restenosis after coronary angioplasty (PTCA). As a regulator of ECM deposition by vascular cells, substantial evidence implicates transforming growth factor-beta1 (TGF-beta1) in the pathogenesis of restenosis. We investigated the effects of intracoronary expression of a transgenic antagonist of TGF-beta1 on luminal loss after PTCA. METHODS AND RESULTS: Porcine coronary arteries were randomized to receive a recombinant adenovirus expressing a secreted form of **TGF -beta** type II receptor (Ad5-RIIs), an adenovirus expressing beta-galactosidase (Ad5-lacZ), or vehicle only by intramural injection at the site of PTCA. Computerized morphometry 28 days after angioplasty revealed a greater minimum luminal area in Ad5-RIIs-injected arteries (1.71+/-0.12 mm(2)) than in the Ad5-lacZ (1.33+/-0.13 mm(2)) or vehicle-only (1.08+/-0.17 mm(2); P=0.010 by ANOVA) groups. This was accompanied by greater areas within the internal (P=0.013) and external (P=0.031) elastic laminae in Ad5-RIIs-treated vessels. Adventitial collagen content at the site of injury was increased in the Ad5-RIIs group, in contrast to decreases in the Ad5-lacZ and vehicle-only groups (P=0.004). CONCLUSIONS: Adenovirus-mediated antagonism of TGF-beta1 at the site of PTCA reduces luminal loss after PTCA by inhibiting constrictive remodeling. Antagonism of TGF-beta1 stimulates the formation of a dense collagenous adventitia, which prevents constrictive remodeling by acting as an external **scaffold**. These findings demonstrate the potential of gene therapy-mediated antagonism of TGF-beta1 as prophylactic therapy for restenosis.

L4 ANSWER 9 OF 19 MEDLINE DUPLICATE 6
2001180447 Document Number: 21082691. PubMed ID: 11214754. Tethered-**TGF-beta** increases **extracellular matrix** production of vascular smooth muscle cells. Mann B K; Schmedlen R H; West J L. (Department of Bioengineering, Rice University, Houston, TX 77251-1892, USA.) BIOMATERIALS, (2001 Mar) 22 (5) 439-44. Journal code: 8100316. ISSN: 0142-9612. Pub. country: England: United Kingdom. Language: English.

AB Biomaterials developed for tissue engineering and wound healing applications need to support robust cell adhesion, yet also need to be replaced by new tissue synthesized by those cells. In order to maintain mechanical integrity of the tissue, the cells must generate sufficient **extracellular matrix** before the **scaffold** is degraded. We have previously shown that materials containing cell adhesive ligands to promote or improve cell adhesion can decrease **extracellular matrix** production (Mann et al., Modification of surfaces with cell adhesion peptides alters **extracellular matrix** deposition. Biomaterials 1999;20:2281-6). Such decreased matrix production by cells in tissue engineering **scaffolds** may result in tissue failure. However, we

have found that TGF-beta1 can be used in **scaffolds** to dramatically increase matrix production. Matrix production by vascular smooth muscle cells grown on adhesive ligand-modified glass surfaces and in PEG hydrogels containing covalently bound adhesive ligands was increased in the presence of 0.04 pmol/ml (1 ng/ml) TGF-beta1. TGF-beta1 can counteract the effect of these adhesive ligands on matrix production; matrix production could be increased even above that observed in the absence of adhesive peptides. Further, TGF-beta1 covalently immobilized to PEG retained its ability to increase matrix production. Tethering TGF-beta1 to the polymer **scaffold** resulted in a significant increase in matrix production over the same amount of soluble TGF-beta1.

L4 ANSWER 10 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001429798 EMBASE Tissue-engineered skin using aggregates of normal human skin fibroblasts and biodegradable material. Furukawa K.S.; Ushida T.; Sakai Y.; Kunii K.; Suzuki M.; Tanaka J.; Tateishi T.. Dr. K.S. Furukawa, Biomedical Engineering Laboratory, Department of Mechanical Engineering, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan. furukawa@tissue.t.u-tokyo.ac.jp. Journal of Artificial Organs 4/4 (353-356) 2001.
Refs: 14.
ISSN: 1434-7229. CODEN: JAORFN. Pub. Country: Japan. Language: English. Summary Language: English.

AB Higher-density inoculation of fibroblasts into a three-dimensional **scaffold** should accelerate wound healing after skin implantation. This study attempted to develop tissue-engineered skin with a higher density of fibroblasts. We first attempted to fabricate three-dimensional high cell-density aggregates (spheroids) of normal human fibroblasts for application to tissue-engineered skin. Our method consisted of rotational shaking with nontreated dishes, decreasing fibroblast-material interactions, and augmenting cell-cell interaction. To prompt aggregate formation, the medium was supplemented with insulin, dexamethasone, ascorbic acid, and basic fibroblast growth factors that potentiate secretion of **extracellular matrices**. Under such improved conditions, fibroblasts were able to form spheroidal aggregates within 24 to 36h of rotational culture. Although the formed aggregates were irregular in shape and were composed of only several cells after 12h, they became almost spheroidal after 24h. The aggregates grew even more round after 36h, and their surfaces became smooth. After 36h of rotational culture, the fibroblast aggregates were collected and reinoculated onto a biodegradable mesh composed of polyglycolic acid coated with collagen. The aggregates were trapped in the material and became attached after 24h. Finally, because transforming growth factor-.beta.(3) (**TGF-.beta.**(3)) is known to accelerate wound healing, we conducted a semiquantitative analysis of **TGF-.beta.**(3) mRNA in both the fibroblast monolayers (two-dimensional culture) and the aggregates (three-dimensional culture). Analysis of **TGF-.beta.**(3) mRNA expression showed that mRNA expression was greater in the fibroblasts of aggregates than in a monolayer. Therefore, our newly developed dermal graft is expected to accelerate wound healing faster than conventional grafts.

L4 ANSWER 11 OF 19 MEDLINE DUPLICATE 7

2000453830 Document Number: 20464676. PubMed ID: 11012081.
Stress-relaxation and contraction of a collagen matrix induces expression of **TGF-beta** and triggers apoptosis in dermal fibroblasts. Varedi M; Tredget E E; Ghahary A; Scott P G. (Department of Surgery, University of Alberta, Edmonton, Canada.) BIOCHEMISTRY AND CELL BIOLOGY, (2000) 78 (4) 427-36. Journal code: 8606068. ISSN: 0829-8211. Pub. country: Canada. Language: English.

AB **Extracellular matrix** serves as a **scaffold** for cells and can also regulate gene expression and ultimately cell behaviour. In this study, we compared the effects of three forms of type I

collagen matrix, which differed only in their mechanical properties, and plastic on the expression of transforming growth factor-beta1 (TGF-beta1), matrix metalloproteinase-1 (collagenase), and type I collagen and on the growth and survival of human dermal fibroblasts. These effects were correlated with alterations in cell morphology and organization of intracellular actin. Cells in detached or stress-relaxed matrices were spherical, lacked stress fibres, and showed increased TGF-beta1 mRNA compared to the cells in anchored collagen matrices or on plastic, which were polygonal or bipolar and formed stress fibres. The levels of **TGF-beta** measured by bioassay were higher in detached and stress-relaxed collagen matrices, than in anchored collagen matrices. Cells on plastic contained little or no immunoreactive **TGF-beta**, while most cells in collagen matrices were stained. The levels of collagenase mRNA were significantly higher in all the collagen matrix cultures compared to those on plastic, but there were no statistically significant differences between them. Levels of mRNA for procollagen type I were not significantly affected by culture in the collagen matrices. Apoptotic fibroblasts were detected by the TUNEL assay in detached (5.7%) and to a lesser extent in stress-relaxed (2.2%) matrices, but none were observed in anchored collagen matrices or on plastic. These results show that alterations in the mechanical properties of matrix can induce the expression of **TGF-beta** and trigger apoptosis in dermal fibroblasts. They further suggest that inability to reorganize this matrix could be responsible for the maintenance of the fibroproliferative phenotype associated with fibroblasts in hypertrophic scarring.

L4 ANSWER 12 OF 19 MEDLINE DUPLICATE 8

2000208036 Document Number: 20208036. PubMed ID: 10743633. [Degree of differentiation of chondrocytes and their pretreatment with platelet-derived-growth factor. Regulating induction of cartilage formation in resorbable tissue carriers in vivo]. Der Differenzierungsgrad von Chondrozyten und ihre Vorbehandlung mit "platelet-derived-growth-factor". Induktionsregulierung der Knorpelbildung in resorbierbaren Gewebetragern in vivo. Lohmann C H; Schwartz Z; Niederauer G G; Boyan B D. (Department of Orthopaedics, University of Texas Health Science Center, San Antonio, USA.. LohmannCH@t-online.de) . ORTHOPADE, (2000 Feb) 29 (2) 120-8. Journal code: 0331266. ISSN: 0085-4530. Pub. country: GERMANY: Germany, Federal Republic of. Language: German.

AB Current methods for articular cartilage repair are unpredictable with respect to clinical success. In the present study, we investigated the ability of cells from articular cartilage, perichondrium, and costochondral resting zone to form new cartilage when loaded onto biodegradable **scaffolds** and implanted into calf muscle pouches of nu/nu mice. Prior in vitro studies showed that platelet derived growth factor-BB (PDGF-BB), but not transforming growth factor beta-1 (**TGF-beta** 1), basic fibroblast growth factor, or bone morphogenetic protein-2 promoted proliferation and **extracellular matrix** sulfation of resting zone chondrocytes without causing the cells to exhibit a hypertrophic chondrocyte phenotype. **TGF-beta** 1 has also been shown to stimulate chondrogenesis by multipotent chondroprogenitor cells like those in the perichondrium. In addition, PDGF-BB has been shown to modulate chondrogensis by resting zone cells implanted in poly(D,L-lactide-co-glycolide) (PLG) **scaffolds** . In the present study we examined whether the cartilage formation is dependent on state of chondrocyte maturation and whether the pretreatment of chondrocytes with growth factors has an influence on the cartilage formation. **Scaffolds** were manufactured from 80% PLG with a 75:25 lactide:glycolide ratio and 20% modified PLG with a 50:50 lactide:glycolide ratio (PLG-H **scaffolds**). For each experimental group, four nude mice received two identical implants, one in each calf muscle resulting in an N = 8 implants: PLG-H **scaffolds** alone;

PLG-H **scaffolds** with cells derived from either the femoral articular cartilage, costochondral periochondrium, or costochondral resting zone cartilage of 125 g male Sprague-Dawley rats; PLG-H **scaffolds** with either articular chondrocytes or resting zone chondrocytes that were pretreated with 37.5 ng/ml rhPDGF-BB for 4 h or 24 h before implantation, or with perichondrial cells treated with PDGF-BB plus 0.22 ng/ml rhTGF beta-1 for 4 h and 24 h. At 4 or 8 weeks after implantation, samples were harvested and analyzed histomorphometrically for new cartilage formed, area of residual implant and area of fibrous connective tissue. Only resting zone cells showed the ability to form new cartilage at a heterotopic site in this study. There was no neocartilage found in nude mice with implants loaded with either articular chondrocytes or perichondrial cells. Pretreatment of resting zone chondrocytes for 4 h prior to implantation significantly increased the amount of newly formed cartilage after 8 weeks and suppressed chondrocyte hypertrophy. The amount of fibrous connective tissue around implants containing either articular chondrocytes or perichondrial cells decreased with time, whereas the amount of fibrous connective tissue around implants containing resting zone chondrocytes pretreated with PDGF-BB was increased. The results showed that resting zone cells can be successfully incorporated into biodegradable porous PLG **scaffolds** and can induce new cartilage formation in a nonweight-bearing site. Articular chondrocytes as well as perichondrial cells did not have the capacity for neochondrogenesis when implanted heterotopically in this model.

L4 ANSWER 13 OF 19 MEDLINE DUPLICATE 9
2000080597 Document Number: 20080597. PubMed ID: 10614934. Modification of surfaces with cell adhesion peptides alters **extracellular matrix** deposition. Mann B K; Tsai A T; Scott-Burden T; West J L. (Department of Bioengineering, Rice University, Houston, TX 77285-1892, USA.) BIOMATERIALS, (1999 Dec) 20 (23-24) 2281-6. Journal code: 8100316. ISSN: 0142-9612. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The goal of the current study was to evaluate matrix protein synthesis by cells cultured on materials that had been modified with cell adhesion ligands. We examined the effects of surface peptide density and of peptides with different affinities on the **extracellular matrix** production of smooth muscle cells, endothelial cells and fibroblasts. While initial adhesion was greatest on the higher density peptide surfaces, all cell types exhibited decreased matrix production on the more highly adhesive surfaces. Similarly, when different peptides were evaluated, matrix production was the lowest on the most adhesive surface and highest on the least adhesive surface. These results suggest that **extracellular matrix** synthesis may be regulated, to some extent, by signal transduction initiated by adhesion events. This may pose limitations for use of bioactive materials as tissue engineering **scaffolds**, as matrix production is an important aspect of tissue formation. However, it may be possible to increase matrix production on highly adhesive surfaces using exogenous factors. **TGF-beta** was shown to increase matrix production by both smooth muscle cells and endothelial cells.

L4 ANSWER 14 OF 19 MEDLINE DUPLICATE 10
1999175323 Document Number: 99175323. PubMed ID: 10074410. Crystal structure of human bone morphogenetic protein-2 at 2.7 A resolution. Scheufler C; Sebald W; Hulsmeyer M. (Physiological Chemistry II, University of Wurzburg, Wurzburg, 97074, Germany.) JOURNAL OF MOLECULAR BIOLOGY, (1999 Mar 19) 287 (1) 103-15. Journal code: 2985088R. ISSN: 0022-2836. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Homodimeric bone morphogenetic protein-2 (BMP-2) is a member of the transforming growth factor beta (**TGF-beta**) superfamily that induces bone formation and regeneration, and determines important steps during early stages of embryonic development in vertebrates and non-vertebrates. BMP-2 can interact with two types of receptor chains, as

well as with proteins of the **extracellular matrix** and several regulatory proteins. We report here the crystal structure of human BMP-2 determined by molecular replacement and refined to an R-value of 24.2 % at 2.7 A resolution. A common **scaffold** of BMP-2, BMP-7 and the **TGF-betas**, i.e. the cystine-knot motif and two finger-like double-stranded beta-sheets, can be superimposed with r. m.s. deviations of around 1 A. In contrast to the **TGF-betas** , the structure of BMP-2 shows differences in the flexibility of the N terminus and the orientation of the central alpha-helix as well as two external loops at the fingertips with respect to the **scaffold**. This is also known from the BMP-7 model. Small secondary structure elements in the loop regions of BMP-2 and BMP-7 seem to be specific for the respective BMP-subgroup. Two identical helix-finger clefts and two distinct cavities located around the central 2-fold axis of the dimer show characteristic shapes, polarity and surface charges. The possible function of these specific features in the interaction of BMP-2 with its binding partners is discussed.

L4 ANSWER 15 OF 19 MEDLINE DUPLICATE 11
1998435862 Document Number: 98435862. PubMed ID: 9764833. The cutaneous microfibrillar apparatus contains latent transforming growth factor-beta binding protein-1 (LTBP-1) and is a repository for latent TGF-beta1.
Raghunath M; Unsold C; Kubitscheck U; Bruckner-Tuderman L; Peters R; Meuli M. (Department of Dermatology, University of Munster, Germany.) JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1998 Oct) 111 (4) 559-64. Journal code: 0426720. ISSN: 0022-202X. Pub. country: United States. Language: English.
AB The transforming growth factors-beta1 and beta2 (**TGF-beta**) stimulate synthesis of **extracellular matrix** proteins in vitro and appear upregulated in fibrotic conditions, in scar formation, and in wound healing. The **extracellular matrix** in turn might also act as a scavenger or repository for **TGF-beta**. We therefore studied the in situ distribution of latent TGF binding protein-1 (LTBP-1) and latent TGF-beta1 on **extracellular matrix** elements of normal human skin and skin regenerating from cultured keratinocyte autografts. We localized both LTBP-1 and latent TGF-beta1 to fibrillin-containing (elastic) microfibrils. Both LTBP-1 and latent TGF-beta1 were already present during the earliest stages of the de novo formation of the microfibrillar apparatus, i.e., on fusiform, randomly oriented microfibrils that later coalesced to form the typical candelabra-like structures in the papillary dermis. We show herewith that LTBP-1 exerts a dual role as a component of fibrillin-microfibrils of the skin and in targeting latent TGF-beta1 to the cutaneous microfibrillar apparatus. Thus, this major connective tissue structure does not only serve as a force bearing element and **scaffold** for elastin deposition in the dermis, but also as an important repository for latent **TGF-beta** in the skin.

L4 ANSWER 16 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 12
1998248104 EMBASE Induction of pulmonary fibrosis in organ-cultured rat lung by cadmium chloride and transforming growth factor-.beta.1. Lin C.-J.; Yang P.-C.; Hsu M.-T.; Yew F.-H.; Liu T.-Y.; Shun C.-T.; Tyan S.- W.; Lee T.-C.. T.-C. Lee, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan,Province of China. bmtcl@ibms.sinica.edu.tw. Toxicology 127/1-3 (157-166) 15 May 1998.
Refs: 44.
ISSN: 0300-483X. CODEN: TXCYAC.
Publisher Ident.: S 0300-483X(98)00025-0. Pub. Country: Ireland. Language: English. Summary Language: English.
AB Cadmium chloride (CdCl2) exposure has been reported to induce pulmonary fibrosis in rats. Accumulating evidence has shown that cytokines play a pivotal role in the excessive production of connective tissue components

in pulmonary fibrosis. In this report, rat lung slice cultures were used to study the synergistic involvement of transforming growth factor-.beta.1 (**TGF- .beta.**1) in CdCl2-induced alveolar fibrosis. Rat lung slices were maintained at the interphase of air and medium on a polyester mesh stretched on a plastic **scaffold**. Treatment of lung slices with 2.5, 5 or 10 .mu.M CdCl2 for 7 days resulted in 85, 40 and 6% respectively for relative survival. Under these culture conditions, CdCl2 alone did not induce alveolar fibrosis in rat lung slices. However, in the presence of 0.5 ng/ml **TGF-.beta.**1, CdCl2 at a dose ranging from 1 to 5 .mu.M increased the thickness of alveolar septa. Furthermore, the thickness of alveolar septa in lung slices treated with CdCl2 was dose-dependently increased by the presence of **TGF-.beta.**1. The thickened alveolar septa were apparently due to the deposition of excessive **extracellular matrix**, as revealed by trichrome stain and ultrastructural examination. Our results also show that fibrogenic activity induced by the combined treatment with CdCl2 and **TGF-.beta.**1 can be reduced by co-treatment with 200 .mu.g/ml .lambda.-carrageenan, a **TGF-.beta.**1 inhibitor. Therefore, the present results indicate that **TGF-.beta.**1 can synergistically stimulate the fibrogenic activity in lung tissue subsequent to CdCl2 injury.

L4 ANSWER 17 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 13

97179549 EMBASE Document No.: 1997179549. Vascular permeability factor/vascular endothelial growth factor inhibits anchorage-disruption-induced apoptosis in microvessel endothelial cells by inducing **scaffold** formation. Watanabe Y.; Dvorak H.F.. Y. Watanabe, Department of Pathology, Beth Israel Hospital, Harvard Medical School, 99 Brookline Avenue, Boston, MA 02215, United States. Experimental Cell Research 233/2 (340-349) 1997.
Refs: 47.
ISSN: 0014-4827. CODEN: ECREAL. Pub. Country: United States. Language: English. Summary Language: English.

AB Survival and proliferation of endothelial cells requires both growth factors and an appropriate **extracellular matrix** to which cells can attach. In the absence of either, endothelial cells rapidly undergo apoptosis. Thus, when human microvascular endothelial cells (HDMEC) are plated on a hydrophobic surface such as untreated polystyrene, they rapidly undergo apoptosis and die. The present study demonstrates that vascular permeability factor/vascular endothelial growth factor (VPF/VEGF), an endothelial cell- selective cytokine, inhibits apoptosis of HDMEC cultured on untreated polystyrene and induces these cells to adhere, spread, and proliferate. VPF/VEGF-induced HDMEC adhesion was time-dependent, required de novo protein synthesis, and was inhibited by a soluble RGD peptide but not by an inhibitor of collagen synthesis. Under the conditions of these experiments, VPF/VEGF downregulated expression of collagen IV and fibronectin but did not change collagen I mRNA levels. VPF/VEGF-induced HDMEC adhesion was inhibited by antibodies to .alpha.v.beta.5 and vitronectin but not by antibodies to .alpha.v.beta.3. Other endothelial growth factors and cytokines such as bFGF, HGF, and **TGF.beta.** did not reproduce the VPF/VEGF effect. We suggest that VPF/VEGF induces endothelial cells to deposit a scaffolding (likely involving vitronectin) that allows them to attach to and proliferate on an otherwise nonsupportive surface (hydrophobic polystyrene) and in this manner serves as both a survival factor and a growth factor.

L4 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1998:82894 Document No.: PREV199800082894. Collagen and heparin matrices for growth factor delivery. Schroeder-Tefft, J. A. (1); Bentz, H.; Estridge, T. D.. (1) Res. Dev., Collagen Corp., 2500 Faber Place, Palo Alto, CA 94303 USA. Journal of Controlled Release, (Dec. 15, 1997) Vol. 49, No. 2-3, pp. 291-298. ISSN: 0168-3659. Language: English.

AB Transforming growth factor-beta 2 (TGF-beta2) loses biological activity under physiological conditions as measured by its loss of activity in phosphate buffered saline (PBS), pH 7.4 at 37degree C. Studies were carried out to determine if TGF-beta2 could be stabilized by the production of a heparin/TGF-beta2 (Hep/TGF-beta2) complex. In vitro studies showed that Hep/TGF-beta2 remained active and TGF-beta2 alone lost activity, when stored for 2 months in PBS at 37degree C, as measured by a Mink lung bioassay. These findings show the utility of using a heparin/TGF-beta2 complex to stabilize the TGF-beta2. Stable Hep/TGF-beta2 complex was mixed with injectable fibrillar collagen for use as a tissue **scaffold** material. Collagen and TGF-beta2 formulations were tested for in vivo activity in a rat subcutaneous model. Forty-five animals were implanted with two injections of fibrillar collagen (FC), fibrillar collagen with heparin and guinea pig serum albumin (FC/Hep/GSA), fibrillar collagen with TGF-beta2 (FC + TGF-beta2), or fibrillar collagen with heparin/TGF-beta2 complex (FC + Hep/**TGF-beta**). Five animals were explanted at day 7, 21 and 42. The FC + Hep/TGF-beta2 formulation and FC + TGF-beta2, admixed formulation both produced increased **extracellular matrix** deposition and activation of cells in vivo. The ability of the FC + Hep/TGF-beta2 complex to recruit fibroblasts and produce new connective tissue locally, demonstrates the TGF-beta2 activity of the FC + Hep/TGF-beta2 complex in vivo.

L4 ANSWER 19 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 14
97216963 EMBASE Document No.: 1997216963. Collagen and heparin matrices for growth factor delivery. Schroeder-Tefft J.A.; Bentz H.; Estridge T.D..
J.A. Schroeder-Tefft, Research and Development, Collagen Corporation, 2500 Faber Place, Palo Alto, CA 94303, United States. jacci-schroeder@collagen.com. Journal of Controlled Release 48/1 (29-33) 1997.
Refs: 19.
ISSN: 0168-3659. CODEN: JCREEC.
Publisher Ident.: S 0168-3659(97)00055-2. Pub. Country: Netherlands.
Language: English. Summary Language: English.

AB Transforming growth factor-beta 2 (**TGF-.beta.**2) loses biological activity under physiological conditions as measured by its loss of activity in phosphate buffered saline (PBS), pH 7.4 at 37.degree.C. Studies were carried out to determine if **TGF-.beta.**2 could be stabilized by the production of a heparin/**TGF-** .**beta.**2 (Hep/**TGF-.beta.**2) complex. In vitro studies showed that Hep/**TGF-.beta.**2 remained active and **TGF-.beta.**2 alone lost activity, when stored for 2 months in PBS at 37.degree.C, as measured by a Mink lung bioassay. These findings show the utility of using a heparin/**TGF-.beta**.2 complex to stabilize the **TGF-.beta.**2. Stable Hep/**TGF-** .**beta.**2 complex was mixed with injectable fibrillar collagen for use as a tissue **scaffold** material. Collagen and **TGF-.beta.**2 formulations were tested for in vivo activity in a rat subcutaneous model. Forty-five animals were implanted with two injections of fibrillar collagen (FC), fibrillar collagen with heparin and guinea pig serum albumin (FC/Hep/GSA), fibrillar collagen with **TGF-.beta.**2 (FC+**TGF-.beta.**2), or fibrillar collagen with heparin/**TGF-.beta.**2 complex (FC+Hep/**TGF-** .**beta.**). Five animals were explanted at day 7, 21 and 42. The FC+Hep/**TGF-.beta.**2 formulation and FC+**TGF-.beta.**2, admixed formulation both produced increased **extracellular matrix** deposition and activation of cells in vivo. The ability of the FC+Hep/**TGF-**.**beta.**2 complex to recruit fibroblasts and produce new connective tissue locally, demonstrates the **TGF-.beta.**2 activity of the FC+Hep/**TGF-.beta.**2 complex in vivo.

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     FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 19:13:46 ON 21 NOV 2002
L1       119034 S EXTRACELLULAR MATRIX
L2         1067 S L1 AND SCAFFOLD
L3           49 S L2 AND TGF BETA
L4           19 DUP REMOVE L3 (30 DUPLICATES REMOVED)

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L5            0 L3 AND BIODEGRADABLE FOAM

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L6           63 L2 AND LINKED

=> s l6 and TGF-beta
L7            1 L6 AND TGF-BETA

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L7   ANSWER 1 OF 1  EMBASE  COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002001005  EMBASE  TGF-.beta.1 up-regulates paxillin
     protein expression in malignant astrocytoma cells: Requirement for a
     fibronectin substrate. Han X.; Stewart J.E. Jr.; Bellis S.L.; Benveniste
     E.N.; Ding Q.; Tachibana K.; Grammer J.R.; Gladson C.L.. C.L. Gladson,
     University of Alabama, LHRB 567, 701 S. 19th Street, Birmingham, AL 35294,
     United States. Gladson@path.uab.edu. Oncogene  20/55 (7976-7986)  29 Nov
     2001.
     Refs: 20.
     ISSN: 0950-9232. CODEN: ONCNES. Pub. Country: United Kingdom. Language:
     English. Summary Language: English.
AB   Cytokines can influence the interactions between members of the integrin
     cell adhesion receptor family and the extracellular
     matrix thereby potentially affecting cell function and promoting
     cell adhesion, growth and migration of malignant astrocytoma tumor cells.
     As malignant astrocytoma cells synthesize TGF-.beta.1
     in vivo, we analysed the effects of TGF-.beta.1 on
     signaling events associated with integrin receptor ligation, focusing on
     the effects on paxillin, a phosphorylated adaptor protein, that acts as a
     scaffold for signaling molecules recruited to focal adhesions.
     TGF-.beta.1-stimulation of primary astrocytes and
     serum-starved U-251MG malignant astrocytoma cells attached to fibronectin
     induced a substantial increase in the levels of paxillin protein (fivefold
     increase at 2.0 ng/ml) in a dose- and time-dependent manner compared to
     the levels observed on plating onto fibronectin in the absence of
     stimulation. In the astrocytoma cells, this resulted in an increase in the
     pool of tyrosine-phosphorylated paxillin, although it did not appear to
     alter the extent of phosphorylation of the paxillin molecules. In
     contrast, in primary astrocytes the protein levels were upregulated in the
     absence of a parallel increase in phosphorylation. The TGF-.
     beta.1-stimulated increase in paxillin levels required ligation of
     the fibronectin receptor, as it was not induced when the cells were plated
     onto vitronectin, collagen or laminin. The increase in the pool of
     paxillin on TGF-.beta.1 stimulation of the
     fibronectin-plated astrocytoma cells was associated with an increase in
     translation, but was not associated with an increase in the steady-state
     levels of paxillin mRNA. Stimulation with TGF-.beta.1
     on a fibronectin substrate increased subsequent attachment and spreading
     of U-251MG cells onto fibronectin and, to a lesser extent, vitronectin,
     but not collagen. Our results indicate that physiologic levels of
     TGF-.beta.1 stimulate the expression of paxillin protein
     at the level of translation through a process that requires engagement of
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the fibronectin receptor, and promotes attachment and spreading of malignant astrocytoma cells on fibronectin.

=> s tissue engineering
L8 6738 TISSUE ENGINEERING

=> s l8 and hydrogel
L9 433 L8 AND HYDROGEL

=> s l9 and TGF-beta
L10 12 L9 AND TGF-BETA

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PROCESSING COMPLETED FOR L10
L11 5 DUP REMOVE L10 (7 DUPLICATES REMOVED)

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L11 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS
2002:157948 Document No. 136:205503 **Tissue engineering** scaffolds promoting matrix protein production. West, Jennifer L.; Mann, Brenda K. (Rice University, USA). PCT Int. Appl. WO 2002016557 A2 20020228, 25 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US26170 20010821. PRIORITY: US 2000-PV226771 20000821.

AB Matrix-enhancing mols., such as **TGF-.beta.**, are conjugated to or immobilized on scaffolds to increase ECM prodn. by cells for **tissue engineering**, tissue regeneration and wound healing applications. The matrix-enhancing mol. is conjugated to a tether, such as polyethylene glycol (PEG) monoacrylate, for attachment to a **tissue engineering** or cell growth scaffold. The matrix-enhancing mol. retains activity after attachment to the scaffold, and causes cells growing in or on the scaffold to increase extracellular matrix (ECM) prodn., without substantially increasing proliferation of the cells, even when the scaffold addnl. contains cell adhesion ligands. The increased ECM produced by the cells aids in maintaining the integrity of the scaffold, particularly when the scaffold is degradable, either by hydrolysis or by enzymic degrdn. For example, TNF.beta. was conjugated to polyethylene glycol by reacting TNF.beta. with acryloyl-PEG-N-hydroxysuccinimide in TRIS buffer (pH 8.5) for 2 h. The mixt. was then lyophilized and stored frozen. Smooth muscle cells were cultured in presence of 0.04 pmol/mL acryloyl-PEG-**TGF.beta.** and prodn. of extracellular matrix protein was evaluated.

L11 ANSWER 2 OF 5 MEDLINE DUPLICATE 1
2002055489 Document Number: 21639375. PubMed ID: 11781011.
Controlled-release of IGF-I and TGF-beta1 in a photopolymerizing **hydrogel** for cartilage **tissue engineering**.
Elisseeff J; McIntosh W; Fu K; Blunk B T; Langer R. (Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02139, USA.) JOURNAL OF ORTHOPAEDIC RESEARCH, (2001 Nov) 19 (6) 1098-104. Journal code: 8404726. ISSN: 0736-0266. Pub. country: United States. Language: English.

AB Photopolymerizing **hydrogel** systems provide a method to encapsulate cells and implant materials in a minimally invasive manner. Controlled release of growth factors in the **hydrogels** may

enhance the ability to engineer tissues. IGF-I and TGF-beta1 were loaded in PLGA microspheres using a double emulsion technique. 125 ng and 200 pg of active IGF-I and **TGF-beta**, respectively, as measured by ELISA, were released over 15 days. The growth factor containing microspheres were photoencapsulated with bovine articular chondrocytes in PEO-based **hydrogels** and incubated in vitro for two weeks. Statistically significant changes in glycosaminoglycan (GAG) production compared to control gels either without microspheres or with blank spheres were observed after a 14 day incubation with IGF-I and IGF-I/**TGF-beta** microspheres combined, with a maximum density of 8.41+/-2.5% wet weight GAG. Total collagen density was low and decreased with the IGF-I/**TGF-beta** microspheres after two weeks incubation, but otherwise remained unchanged in all other experimental groups. Cell content increased 10-fold to 0.18+/-0.056 x 10(6) cells/mg wet weight and extracellular matrix (ECM) staining by H&E increased in **hydrogels** with IGF-I/**TGF-beta** microspheres. In conclusion, photoencapsulation of microspheres in PEO-based **hydrogels** provides a method to deliver molecules such as growth factors in porous **hydrogel** systems.

L11 ANSWER 3 OF 5 MEDLINE DUPLICATE 2

2001180447 Document Number: 21082691. PubMed ID: 11214754. Tethered-**TGF-beta** increases extracellular matrix production of vascular smooth muscle cells. Mann B K; Schmedlen R H; West J L. (Department of Bioengineering, Rice University, Houston, TX 77251-1892, USA.) BIOMATERIALS, (2001 Mar) 22 (5) 439-44. Journal code: 8100316. ISSN: 0142-9612. Pub. country: England: United Kingdom. Language: English.

AB Biomaterials developed for **tissue engineering** and wound healing applications need to support robust cell adhesion, yet also need to be replaced by new tissue synthesized by those cells. In order to maintain mechanical integrity of the tissue, the cells must generate sufficient extracellular matrix before the scaffold is degraded. We have previously shown that materials containing cell adhesive ligands to promote or improve cell adhesion can decrease extracellular matrix production (Mann et al., Modification of surfaces with cell adhesion peptides alters extracellular matrix deposition. Biomaterials 1999;20:2281-6). Such decreased matrix production by cells in **tissue engineering** scaffolds may result in tissue failure. However, we have found that TGF-beta1 can be used in scaffolds to dramatically increase matrix production. Matrix production by vascular smooth muscle cells grown on adhesive ligand-modified glass surfaces and in PEG **hydrogels** containing covalently bound adhesive ligands was increased in the presence of 0.04 pmol/ml (1 ng/ml) TGF-beta1. TGF-beta1 can counteract the effect of these adhesive ligands on matrix production; matrix production could be increased even above that observed in the absence of adhesive peptides. Further, TGF-beta1 covalently immobilized to PEG retained its ability to increase matrix production. Tethering TGF-beta1 to the polymer scaffold resulted in a significant increase in matrix production over the same amount of soluble TGF-beta1.

L11 ANSWER 4 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2000:288137 Document No.: PREV200000288137. The importance of drug delivery systems in **tissue engineering**. Tabata, Yasuhiko (1). (1) Institute for Frontier Medical Sciences, Kyoto University, 53 Kawara-cho Shogoin Sakyo-ku, Kyoto, 606-8507 Japan. Pharmaceutical Science & Technology Today, (March, 2000) Vol. 3, No. 3, pp. 80-89. print. ISSN: 1461-5347. Language: English. Summary Language: English.

AB **Tissue engineering** is designed to regenerate natural tissues or to create biological substitutes for defective or lost tissues and organs through the use of cells. In addition to cells and their scaffolds, growth factors are required to promote tissue regeneration. Indeed, growth factor-induced vascularization is effective in supplying the oxygen and nutrients necessary for the survival of transplanted cells

in organ substitution. However, growth factors have poor in vivo stability and so the biological effects are often unpredictable unless the delivery system is contrived. This review provides several examples to emphasize the importance of drug delivery systems in **tissue engineering**.

L11 ANSWER 5 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 3
1999416720 EMBASE Growth factor release from gelatin **hydrogel** for **tissue engineering**. Yamamoto M.; Tabata Y.; Ikada Y.. Y. Ikada, Inst. for Frontiér Medical Sciences, Kyoto University, 53 Kawara-cho Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Journal of Bioactive and Compatible Polymers 14/6 (474-489) 1999.
Refs: 32.
ISSN: 0883-9115. CODEN: JBCPEV. Pub. Country: United States. Language: English. Summary Language: English.

AB One of the key technologies for regeneration of damaged and lost tissue is the sustained release of biologically active growth factors. The present study was undertaken to investigate sorption and desorption of various growth factors from biodegradable **hydrogels** prepared through glutaraldehyde crosslinking of gelatin with isoelectric points (IEPs) of 5.0 and 9.0, which are named 'acidic' and 'basic' gelatins, respectively, based on their overall charge. Basic bFGF and **TGF-.beta**.1 were markedly sorbed with time in the acidic gelatin **hydrogels**, while less sorption took place in the basic gelatin **hydrogels**. This behavior was explained in terms of an electrostatic interaction between the basic growth factors and the acidic gelatin. However, BMP-2 was sorbed into the acidic gelatin **hydrogel** to alesser extent than the other two growth factors, even though its IEP is also greater than 7.0. An in vivo experiment revealed that the acidic gelatin **hydrogel** was degraded with time, while growth factors were retained in the body for a longer time period as the in vitro sorption to the acidic gelatin **hydrogel** was larger. These findings indicate that the growth factors ionically complexed to the acidic gelatin **hydrogel** were released in vivo as a result of **hydrogel** degradation. Furthermore, animal experiments revealed that the biological performance of growth factors was enhanced by their sustained release, in marked contrast to the growth factors administered in the solution form.

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In a multifile environment, a format can only be used if it is valid
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In a multifile environment, a format can only be used if it is valid
in at least one of the files.  Refer to file specific help messages
or the STNGUIDE file for information on formats available in
individual files.
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L11 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2002 ACS

AB Matrix-enhancing mols., such as **TGF-.beta.**, are conjugated to or immobilized on scaffolds to increase ECM prodn. by cells

for **tissue engineering**, tissue regeneration and wound healing applications. The matrix-enhancing mol. is conjugated to a tether, such as polyethylene glycol (PEG) monoacrylate, for attachment to a **tissue engineering** or cell growth scaffold. The matrix-enhancing mol. retains activity after attachment to the scaffold, and causes cells growing in or on the scaffold to increase extracellular matrix (ECM) prodn., without substantially increasing proliferation of the cells, even when the scaffold addnl. contains cell adhesion ligands. The increased ECM produced by the cells aids in maintaining the integrity of the scaffold, particularly when the scaffold is degradable, either by hydrolysis or by enzymic degrdn. For example, TNF.beta. was conjugated to polyethylene glycol by reacting TNF.beta. with acryloyl-PEG-N-hydroxysuccinimide in TRIS buffer (pH 8.5) for 2 h. The mixt. was then lyophilized and stored frozen. Smooth muscle cells were cultured in presence of 0.04 pmol/mL acryloyl-PEG-**TGF.beta**. and prodn. of extracellular matrix protein was evaluated.

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L1       119034 S EXTRACELLULAR MATRIX
L2         1067 S L1 AND SCAFFOLD
L3           49 S L2 AND TGF BETA
L4           19 DUP REMOVE L3 (30 DUPLICATES REMOVED)
L5            0 S L3 AND BIODEGRADABLE FOAM
L6           63 S L2 AND LINKED
L7            1 S L6 AND TGF-BETA
L8         6738 S TISSUE ENGINEERING
L9          433 S L8 AND HYDROGEL
L10          12 S L9 AND TGF-BETA
L11           5 DUP REMOVE L10 (7 DUPLICATES REMOVED)

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L12          44 L9 AND DENSITY

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L13           0 L12 AND 2000-6000

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L14          20 DUP REMOVE L12 (24 DUPLICATES REMOVED)

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L14  ANSWER 1 OF 20     MEDLINE                              DUPLICATE 1
2002461310  Document Number: 22208129.    PubMed ID: 12219821.
     Photoencapsulation of osteoblasts in injectable RGD-modified PEG
     hydrogels for bone tissue engineering. Burdick
     Jason A; Anseth Kristi S. (Department of Chemical Engineering, University
     of Colorado, Boulder 80309-0424, USA. ) BIOMATERIALS, (2002 Nov) 23 (22)
     4315-23.  Journal code: 8100316. ISSN: 0142-9612. Pub. country: England:
     United Kingdom. Language: English.
AB   Poly(ethylene glycol) (PEG) hydrogels were investigated as
     encapsulation matrices for osteoblasts to assess their applicability in
     promoting bone tissue engineering. Non-adhesive
     hydrogels were modified with adhesive Arg-Gly-Asp (RGD) peptide
     sequences to facilitate the adhesion, spreading, and, consequently,
     cytoskeletal organization of rat calvarial osteoblasts. When attached to
     hydrogel surfaces, the density and area of osteoblasts
     attached were dramatically different between modified and unmodified
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hydrogels. A concentration dependence of RGD groups was observed, with increased osteoblast attachment and spreading with higher RGD concentrations, and cytoskeleton organization was seen with only the highest peptide **density**. A majority of the osteoblasts survived the photoencapsulation process when gels were formed with 10% macromer, but a decrease in osteoblast viability of approximately 25% and 38% was seen after 1 day of in vitro culture when the macromer concentration was increased to 20 and 30wt%, respectively. There was no statistical difference in cell viability when peptides were added to the network. Finally, mineral deposits were seen in all **hydrogels** after 4 weeks of in vitro culture, but a significant increase in mineralization was observed upon introduction of adhesive peptides throughout the network.

L14 ANSWER 2 OF 20 MEDLINE DUPLICATE 2

2002200613 Document Number: 21885865. PubMed ID: 11888325. Synthesis of in situ cross-linkable macroporous biodegradable poly(propylene fumarate-co-ethylene glycol) **hydrogels**. Behravesh Esfandiar; Jo Seongbong; Zygourakis Kyriacos; Mikos Antonios G. (Department of Bioengineering, Rice University, MS-142, PO Box 1892, Houston, Texas 77251-1892, USA.) Biomacromolecules, (2002 Mar-Apr) 3 (2) 374-81. Journal code: 100892849. ISSN: 1525-7797. Pub. country: United States. Language: English.

AB This study describes a synthesis method of biodegradable macroporous **hydrogels** suitable as in situ cross-linkable biomaterials. Macroporous **hydrogels** were based on poly(propylene fumarate-co-ethylene glycol) and prepared via coupled free radical and pore formation reactions. Cross-linking was initiated by a pair of redox initiators, ammonium persulfate and L-ascorbic acid. Pores were formed by the reaction between L-ascorbic acid and sodium bicarbonate, a basic component, which evolved carbon dioxide. Sol fraction of the **hydrogels** was varied from 0.06 +/- 0.01 to 0.64 +/- 0.01. A stereological approach was used to analyze the morphological properties of the macroporous **hydrogels** by relating the morphological properties of thin sections to the original three-dimensional macroporous **hydrogel**. Prepared macroporous **hydrogels** had porosities between 0.43 +/- 0.08 and 0.84 +/- 0.02 and surface area **densities** between 55 +/- 3 and 108 +/- 7 cm(-1). Sodium bicarbonate concentration had the greatest effect on both the porosity and surface area **density**. The effect of copolymer formulation on the porosity and surface area **density** was insignificant. From thin sections of the macroporous **hydrogels**, the profile size distributions were determined as an estimate of the pore size distribution. Two formulations synthesized with varying L-ascorbic acid concentration of 0.05 and 0.1 M had median profile sizes of 50-100 and 150-200 microm, respectively. This novel synthesis method allows for the in situ cross-linking of biodegradable macroporous **hydrogels** with morpholological properties suitable for consideration as an injectable **tissue engineering** scaffold.

L14 ANSWER 3 OF 20 MEDLINE DUPLICATE 3

2002122328 Document Number: 21846324. PubMed ID: 11857427. Alginate type and RGD **density** control myoblast phenotype. Rowley Jon A; Mooney David J. (Department of Biomedical Engineering, University of Michigan, Colleges of Engineering and Dentistry, Ann Arbor, Michigan, USA.) JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, (2002 May) 60 (2) 217-23. Journal code: 0112726. ISSN: 0021-9304. Pub. country: United States. Language: English.

AB Alginates are being increasingly used for cell encapsulation and **tissue engineering** applications; however, these materials cannot specifically interact with mammalian cells. We have covalently modified alginates of varying monomeric ratio with RGD-containing cell adhesion ligands using carbodiimide chemistry to initiate cell adhesion to these polymers. We hypothesized that we could

control the function of cells adherent to RGD-modified alginate **hydrogels** by varying alginate polymer type and cell adhesion ligand **density**, and we have addressed this possibility by studying the proliferation and differentiation of C2C12 skeletal myoblasts adherent to these materials. RGD **density** on alginates of varying monomeric ratio could be controlled over several orders of magnitude, creating a range of surface **densities** from 1-100 fmol/cm(2). Myoblast adhesion to these materials was specific to the RGD ligand, because adhesion could be competed away with soluble RGD in a dose-dependent manner. Myoblast proliferation and differentiation could be regulated by varying the alginate monomeric ratio and the **density** of RGD ligands at the substrate surface, and specific combinations of alginate type and RGD **density** were required to obtain efficient myoblast differentiation on these materials.
Copyright 2002 Wiley Periodicals, Inc. J Biomed Mater Res 60: 217-223, 2002; DOI 10.1002/jbm.1287

L14 ANSWER 4 OF 20 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4
2002201848 EMBASE Modulation of marrow stromal osteoblast adhesion on biomimetic oligo[poly(ethylene glycol) fumarate] **hydrogels** modified with Arg-Gly-Asp peptides and a poly(ethylene glycol) spacer.
Shin H.; Jo S.; Mikos A.G.. A.G. Mikos, Department of Bioengineering, Rice University, 6100 Main, Houston, TX 77005-1892, United States. mikos@rice.edu. Journal of Biomedical Materials Research 61/2 (169-179) 2002.
Refs: 30.
ISSN: 0021-9304. CODEN: JBMRBG. Pub. Country: United States. Language: English. Summary Language: English.
AB Novel oligo[poly(ethylene glycol) fumarate] (OPF) **hydrogels** functionalized with cell adhesion peptides were prepared, and the effects of incorporated peptide **density** and macromolecular structure of **hydrogels** on attachment and morphology of marrow stromal cells (MSCs) were evaluated. Poly(ethylene glycol) (PEG; number average molecular weight of 930, 2860, and 6090) was used to synthesize OPF. A model peptide, Gly-Arg-Gly-Asp (GRGD), was incorporated into OPF **hydrogels** after being coupled to acrylated PEG of molecular weight 3400. The increase of incorporated peptide concentration enhanced MSC attachment to OPF **hydrogels** of PEG of molecular weight of 930 and 2860. However, the number of attached MSCs to OPF **hydrogels** of PEG (molecular weight 6090) remained constant regardless of the peptide **density**. The length of PEG in OPF also influenced cell attachment. When 1.mu.mole peptide/g **hydrogel** was incorporated into the OPF **hydrogels**, the degree of cell attachment at 12 h relative to the initial seeding **density** was 93.9 .+-. 5.9%, 64.7 .+-. 8.2%, and 9.3 .+-. 6.6% for OPF **hydrogels** prepared with PEG of molecular weights of 930, 2860, and 6090, respectively. However, the crosslinking **density** of **hydrogels** did not significantly affect cell attachment. The interaction was sequence specific, in that MSC attachment to GRGD-modified **hydrogels** was competitively inhibited when cells were incubated in the presence of 0.5 mM soluble GRGD before cell seeding. These results suggest that we can modulate MSC attachment to OPF **hydrogels** by altering the peptide **density** and the molecular structure of OPF **hydrogels**. .COPYRGT. 2002 Wiley Periodicals, Inc.

L14 ANSWER 5 OF 20 MEDLINE DUPLICATE 5
2002103796 Document Number: 21823893. PubMed ID: 11835163. Cell adhesion peptides alter smooth muscle cell adhesion, proliferation, migration, and matrix protein synthesis on modified surfaces and in polymer scaffolds.
Mann Brenda K; West Jennifer L. (Rice University, Department of Bioengineering, P.O. Box 1892, MS-142, Houston, Texas 77251-1892, USA.)
JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, (2002 Apr) 60 (1) 86-93.
Journal code: 0112726. ISSN: 0021-9304. Pub. country: United States.

Language: English.

AB The effects of cell adhesion peptides (RGDS, KQAGDV, VAPG) on vascular smooth muscle cells grown on modified surfaces and in **tissue-engineering** scaffolds were examined. Cells were more strongly adhered to surfaces modified with adhesive ligands than to control surfaces (no ligand or a nonadhesive ligand). Cell migration was higher on surfaces with 0.2 nmol/cm(2) of adhesive ligand than on control surfaces, but it was lower on surfaces with 2.0 nmol/cm(2) of adhesive ligand than it was on control surfaces. Further, cell proliferation was lower on adhesive surfaces than it was on control surfaces, and it decreased as the ligand **density** increased. Similarly, in the peptide-grafted **hydrogel** scaffolds, cell proliferation was lower in scaffolds containing the adhesive peptides than it was in control scaffolds. After 7 days of culture, more collagen per cell was produced in control scaffolds than in scaffolds containing adhesive peptides. In addition, collagen production decreased in the scaffolds as the ligand concentration increased. While modification of a surface or scaffold material with adhesive ligands initially increases cell attachment, it may be necessary to optimize cell adhesion simultaneously with proliferation, migration, and matrix production.
 J Biomed Mater Res 60: 86-93, 2002

L14 ANSWER 6 OF 20 CAPLUS

2002:617853 Photopolymerization of poly(vinyl alcohol) and poly(ethylene glycol)-based macromers to produce cross linked, degradable **hydrogels** with controlled transport properties. Martens, Penny; Bryant, Stephanie J.; Anseth, Kristi S. (Department of Chemical Engineering, University of Colorado, Boulder, CO, 80309, USA). Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002, MACR-014. American Chemical Society: Washington, D. C. (English) 2002. CODEN: 69CZPZ.

AB Degradable **hydrogel** networks are potentially useful for a variety of biomedical applications, such as drug delivery and **tissue engineering**, where the transport of mols. can be controlled by the network structure and degrdn. behavior. Poly(vinyl alc.) (PVA) macromers contg. photocrosslinkable pendant acrylate groups tethered to the PVA by hydrolytically degradable ester linkages were synthesized. Changing the PVA macromer functionality, no. of degradable linkages, and the processing conditions produced gels with degrdn. times ranging from 1 to 180 days. The release of a photoencapsulated model protein, bovine serum albumin, was monitored in a 10-day degrading gel, which correlated to changes in the network structure. Furthermore, copolymn. of these multifunctional macromers with dimethacrylated poly(ethylene glycol) (PEG) produced networks with readily controlled crosslinking **densities** and degrdn. profiles. The PVA-PEG macromer mixt. was used to successfully photoencapsulate chondrocytes, and the controlled degrdn. enabled the prodn., secretion, and uniform distribution of proteoglycans after 2 wk in vitro.

L14 ANSWER 7 OF 20 MEDLINE

2002033616 Document Number: 21594573. PubMed ID: 11759015. Cell-interactive alginate **hydrogels** for bone **tissue engineering**. Alsberg E; Anderson K W; Albeiruti A; Franceschi R T; Mooney D J. (Department of Biomedical Engineering, University of Michigan, Ann Arbor 48109-2136, USA.) JOURNAL OF DENTAL RESEARCH, (2001 Nov) 80 (11) 2025-9. Journal code: 0354343. ISSN: 0022-0345. Pub. country: United States. Language: English.

AB There is significant interest in the development of injectable carriers for cell transplantation to engineer bony tissues. In this study, we hypothesized that adhesion ligands covalently coupled to **hydrogel** carriers would allow one to control pre-osteoblast cell attachment, proliferation, and differentiation. Modification of alginate with an RGD-containing peptide promoted osteoblast adhesion and spreading, whereas

minimal cell adhesion was observed on unmodified **hydrogels**. Raising the adhesion ligand **density** increased osteoblast proliferation, and a minimum ligand **density** (1.5-15 femtomoles/cm2) was needed to elicit this effect. MC3T3-E1 cells demonstrated increased osteoblast differentiation with the peptide-modified **hydrogels**, as confirmed by the up-regulation of bone-specific differentiation markers. Further, transplantation of primary rat calvarial osteoblasts revealed statistically significant increases of in vivo bone formation at 16 and 24 weeks with G4RGDY-modified alginate compared with unmodified alginate. These findings demonstrate that biomaterials may be designed to control bone development from transplanted cells.

L14 ANSWER 8 OF 20 MEDLINE DUPLICATE 6
2002055489 Document Number: 21639375. PubMed ID: 11781011.
Controlled-release of IGF-I and TGF-beta1 in a photopolymerizing **hydrogel** for cartilage **tissue engineering**.
Elisseeff J; McIntosh W; Fu K; Blunk B T; Langer R. (Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02139, USA.) JOURNAL OF ORTHOPAEDIC RESEARCH, (2001 Nov) 19 (6) 1098-104. Journal code: 8404726. ISSN: 0736-0266. Pub. country: United States. Language: English.
AB Photopolymerizing **hydrogel** systems provide a method to encapsulate cells and implant materials in a minimally invasive manner. Controlled release of growth factors in the **hydrogels** may enhance the ability to engineer tissues. IGF-I and TGF-beta1 were loaded in PLGA microspheres using a double emulsion technique. 125 ng and 200 pg of active IGF-I and TGF-beta, respectively, as measured by ELISA, were released over 15 days. The growth factor containing microspheres were photoencapsulated with bovine articular chondrocytes in PEO-based **hydrogels** and incubated in vitro for two weeks. Statistically significant changes in glycosaminoglycan (GAG) production compared to control gels either without microspheres or with blank spheres were observed after a 14 day incubation with IGF-I and IGF-I/TGF-beta microspheres combined, with a maximum **density** of 8.41+/-2.5% wet weight GAG. Total collagen **density** was low and decreased with the IGF-I/TGF-beta microspheres after two weeks incubation, but otherwise remained unchanged in all other experimental groups. Cell content increased 10-fold to 0.18+/-0.056 x 10(6) cells/mg wet weight and extracellular matrix (ECM) staining by H&E increased in **hydrogels** with IGF-I/TGF-beta microspheres. In conclusion, photoencapsulation of microspheres in PEO-based **hydrogels** provides a method to deliver molecules such as growth factors in porous **hydrogel** systems.

L14 ANSWER 9 OF 20 MEDLINE DUPLICATE 7
2002004721 Document Number: 21625433. PubMed ID: 11749736. Cultured chondrocytes produce injectable tissue-engineered cartilage in **hydrogel** polymer. Passaretti D; Silverman R P; Huang W; Kirchhoff C H; Ashiku S; Randolph M A; Yaremchuk M J. (Division of Plastic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA.) TISSUE ENGINEERING, (2001 Dec) 7 (6) 805-15. Journal code: 9505538. ISSN: 1076-3279. Pub. country: United States. Language: English.
AB The purpose of this study was to determine if chondrocytes cultured through several subcultures at very low plating **density** would produce new cartilage matrix after being reimplanted in vivo with or without a **hydrogel** polymer scaffold. Chondrocytes were initially plated in low-**density** monolayer culture, grown to confluence, and passaged four times. After each passage cells were suspended in purified porcine fibrinogen and injected into the subcutaneous space of nude mice while simultaneously polymerizing with thrombin to reach a final concentration of 40 million cells/cc. Controls were made by injecting fresh, uncultured cells with fibrin polymer and by injecting the cultured cells in saline (without polymer). All samples were harvested at 6 weeks.

When injected in polymer, both fresh cells and cells that had undergone only one passage in culture produced cartilaginous nodules. Cultured cells did not produce cartilage, regardless of length of time spent in culture, when injected without polymer. Cartilage was also not recovered from samples with cells kept in culture for longer than one passage, even when provided with a polymer matrix. All samples harvested were subjected to histological analysis and assayed for total DNA, glycosaminoglycan (GAG), and type II collagen. There was histological evidence of cartilage in the groups that used fresh cells and cultured cells suspended in fibrin polymer that only underwent one passage. No other group contained areas that would be consistent with cartilage histologically. All experimental samples had a higher percent of DNA than native swine cartilage, and there was no statistical difference between the DNA content of the groups containing cultured or fresh cells in fibrin polymer. Whereas the GAG content of native cartilage was 8.39% of dry weight and fresh cells in fibrin polymer was 12.85%, cultured cells in fibrin polymer never exceded the 2.48% noted from first passage cells. In conclusion, this study demonstrates that porcine chondrocytes that have been cultured in monolayer for one passage will produce cartilage in vivo when suspended in fibrin polymer.

L14 ANSWER 10 OF 20 MEDLINE DUPLICATE 8
2001304056 Document Number: 20584385. PubMed ID: 11150454. Fetal **tissue engineering**: diaphragmatic replacement. Fauza D O; Marler J J; Koka R; Forse R A; Mayer J E; Vacanti J P. (Harvard Center for Minimally Invasive Surgery and the Departments of Surgery, Children's Hospital and Harvard Medical School, Boston, MA, USA.) JOURNAL OF PEDIATRIC SURGERY, (2001 Jan) 36 (1) 146-51. Journal code: 0052631. ISSN: 0022-3468. Pub. country: United States. Language: English.

AB BACKGROUND/PURPOSE: Prosthetic repair of congenital diaphragmatic hernia has been associated with high complication rates. This study was aimed at applying fetal **tissue engineering** to diaphragmatic replacement. METHODS: Fetal lambs underwent harvest of skeletal muscle specimens. Once expanded in vitro, fetal myoblasts were suspended in a collagen **hydrogel** submitted to controlled radial tension. The construct was then placed in a bioreactor. After birth, all animals underwent creation of 2 diaphragmatic defects. One defect was repaired with the autologous-engineered construct placed in between 2 acellular supporting membranes and the other with an identical construct but without any cells. Each animal was its own control (graft, n = 10). Animals were killed at different time-points postimplantation for histologic examination. Statistical analysis was by analysis of variance (ANOVA). RESULTS: Fetal myoblasts expanded up to twice as fast as neonatal cells. **Hydrogel**-based radial tension enhanced construct architecture by eliciting cell organization within the scaffold. No eventration was present in 4 of 5 engineered constructs but in 0 of 5 acellular grafts (P<.05). At harvest, engineered constructs were thick and histologically resembled normal skeletal muscle, whereas acellular grafts were thin, floppy, and showed low cell **density** with increased fibrosis. CONCLUSIONS: Unlike acellular grafts, engineered cellular diaphragmatic constructs are anatomically and histologically similar to normal muscle. Fetal **tissue engineering** may be a viable alternative for diaphragmatic replacement.

L14 ANSWER 11 OF 20 MEDLINE
2002092740 Document Number: 21673041. PubMed ID: 11812315. A study of injectable autologous **tissue engineering** cartilage. Yang W; Li S; Chen F. (Department of Oral and Maxillofacial Surgery, College of Stomatology, Fourth Military Medical University, Xi'an 710032, China.) CHUNG-HUA KOU CHIANG I HSUEH TSA CHIH CHINESE JOURNAL OF STOMATOLOGY, (2001 Mar) 36 (2) 102-4. Journal code: 8711066. ISSN: 1002-0098. Pub. country: China. Language: Chinese.

AB OBJECTIVE: To study the regeneration of injectable autologous cartilage in

New Zealand rabbits model. METHODS: Chondrocytes were harvested from auricle of New Zealand rabbits. The cells were mixed with sodium alginate (SA) and temperature dependent synthetic **hydrogel** (TDSH) to generate final cellular **density** of 50 x 10(9)/L, and then the chondrocytes-SA and chondrocytes-TDSH composites were injected into the dorsal subcutaneous tissue of New Zealand rabbits with form of autologous cells grafts respectively. The specimen and histology were observed in the process of cartilage fabrication in 4, 8, 12 weeks. RESULTS: Four weeks after injection, the hard knobbles were formed subcutaneously. Eight and twelve weeks after injection, the knobbles was much harder and showed the appearance of cartilage. In histological analysis, the immature cartilage can be observed after 4 weeks. In the eight and twelve weeks, the mature cartilage was formed and showed strong GAG positive expressed by safranine-O. CONCLUSIONS: Neocartilage could be regenerated through injection of alginate and synthetic **hydrogel** mixed with chondrocytes. Using **tissue-engineering** methods, Injectable cartilage may have great potential of clinical use in the future.

L14 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2002 ACS

2001:661943 Document No. 136:284293 Degradation kinetics influence ECM production of photoencapsulated chondrocytes in PEG-based **hydrogels**. Bryant, Stephanie J.; Durand, Kevin L.; Anseth, Kristi S. (Department of Chemical Engineering and the Howard Hughes Medical Institute, University of Colorado, Boulder, CO, 80309-0424, USA). Polymer Preprints (American Chemical Society, Division of Polymer Chemistry), 42(2), 86-87 (English) 2001. CODEN: ACPPAY. ISSN: 0032-3934. Publisher: American Chemical Society, Division of Polymer Chemistry.

AB The role of **hydrogel** crosslinking d. and degrdn. kinetics on the ability of photoencapsulated chondrocytes to produce cartilaginous tissue was studied. Poly(ethylene glycol)(PEG) **hydrogels** prepd. by photopolymg. the poly(ethylene glycol) dimethacrylate macromer and/or poly(lactic acid)-.beta.-poly(ethylene)-.beta.-poly(lactic acid) macromer at different concns. Cell constructs were analyzed for proteoglycans and collagen. Biochem. compn. of the neocartilaginous tissue of encapsulated chondrocytes were analyzed at 2 and 4 wk and examd. as a function of the gel properties. Proteoglycans (GAG) mols. in more densely crosslinked gels were retained in the pericellular regions. Results showed the impact of **hydrogel** structure on the diffusion and distribution of GAG in the cell-**hydrogel** construct. Degrdn., esp. the time scale for complete degrdn. and the overall mass loss or erosion profile was an important criteria in **hydrogel** scaffold design for **tissue engineering** cartilage and spatial distribution control of the ECM components.

L14 ANSWER 13 OF 20 MEDLINE DUPLICATE 9

2001072895 Document Number: 20566497. PubMed ID: 11115280. Internal support of tissue-engineered cartilage. Arevalo-Silva C A; Eavey R D; Cao Y; Vacanti M; Weng Y; Vacanti C A. (Department of Otolaryngology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114, USA.) ARCHIVES OF OTOLARYNGOLOGY -- HEAD AND NECK SURGERY, (2000 Dec) 126 (12) 1448-52. Journal code: 8603209. ISSN: 0886-4470. Pub. country: United States. Language: English.

AB BACKGROUND: Auricles previously created by **tissue engineering** in nude mice used a biodegradable internal scaffold to maintain the desired shape of an ear. However, the biodegradable scaffold incited a compromising inflammatory response in subsequent experiments in immunocompetent animals. OBJECTIVE: To test the hypothesis that tissue-engineered autologous cartilage can be bioincorporated with a nonreactive, permanent endoskeletal scaffold. MATERIALS AND METHODS: Auricular elastic cartilage was harvested from Yorkshire swine. The chondrocytes were isolated and suspended into a **hydrogel** (Pluronic F-127) at a cell concentration of 5 x 10(7) cells/mL.

Nonbiodegradable endoskeletal scaffolds were formed with 1 of 5 polymers: (1) high-**density** polyethylene, (2) soft acrylic, (3) polymethylmethacrylate, (4) extrapurified Silastic, and (5) conventional Silastic. Three groups were studied: (1) a control group using only the 5 polymers, (2) the 5 polymers enveloped by Pluronic F-127 only, and (3) the implants coated with Pluronic F-127 seeded with chondrocytes. All constructs were implanted subdermally; implants containing cells were implanted into the same animal from which the cells had been islolated. The implants were harvested after 8 weeks of in vivo culture and histologically analyzed. RESULTS: Only implants coated by **hydrogel** plus cells generated healthy new cartilage. With 3 polymers (high-**density** polyethylene, acrylic, and extrapurified Silastic), the coverage was nearly complete by elastic cartilage, with minimal fibrocartilage and minimal to no inflammatory reaction. The Food and Drug Administration-approved conventional Silastic implants resulted in fragments of fibrous tissue mixed with elastic cartilage plus evidence of chronic inflammation. The polymethylmethacrylate implant was intermediate in the amount of cartilage formed and degree of inflammation. CONCLUSIONS: This pilot technique combining tissue-engineered autologous elastic cartilage with a permanent biocompatible endoskeleton demonstrated success in limiting the inflammatory response to the scaffold, especially to high-**density** polyethylene, acrylic, and extrapurified Silastic. This model facilitates the potential to generate tissue of intricate shape, such as the human ear, by internal support. Arch Otolaryngol Head Neck Surg. 2000;126:1448-1452

L14 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2002 ACS

2000:334773 Synthesis and characterization of elastin-mimetic protein gels for use in biomedical applications.. McMillan, R. Andrew; Conticello, Vincent P. (Department of Chemistry, Emory University, Atlanta, GA, 30322, USA). Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000, POLY-583. American Chemical Society: Washington, D. C. (English) 2000. CODEN: 69CLAC.

AB In order to elucidate the effect of uniformity of mol. architecture on gel properties, an approx. 90 kDa protein polymer poly(Lys-25) based on tandem repeats of the elastin-mimetic sequence [(Val-Pro-Gly-Val-Gly)4(Val-Pro-Gly-Lys-Gly)] was synthesized using genetic engineering and microbial protein expression. The polymer was crosslinked into gels in DMSO or aq. phosphate buffer by reacting derivs. of homobifunctional N-hydroxysuccinimidylsuberate esters with the nucleophilic amino group of the regularly placed lysine residues. The **hydrogels** exhibited a reversible temp. dependant expansion and contraction due to the inverse temp. transition of the poly(Lys-25) backbone. Characterization of crosslink d. was performed using quant. CP MAS 15N NMR, and gel morphol. was examd. with SEM. Studies revealed differences in crosslink **densities** and solvent dependent morphologies of gels formed under various conditions. Uses for the environmentally responsive **hydrogels** as biomedical materials for drug delivery and **tissue engineering** are discussed.

L14 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2002 ACS

1999:408115 Document No. 131:175029 Fabrication of porous gelatin scaffolds for **tissue engineering**. Kang, Hye-Won; Tabata, Yasuhiko; Ikada, Yoshito (Institute Frontier Medical Sciences, Kyoto Univ., Sakyo-ku, Kyoto, 606-8507, Japan). Biomaterials, 20(14), 1339-1344 (English) 1999. CODEN: BIMADU. ISSN: 0142-9612. Publisher: Elsevier Science Ltd..

AB A novel method which employs water present in swollen **hydrogels** as a porogen for shape template was suggested for prepg. porous materials. Biodegradable **hydrogels** were prepd. by crosslinking of gelatin with glutaraldehyde in aq. soln., followed by rinsing and washing. After freezing the swollen **hydrogels**, the ice formed within the **hydrogel** network was sublimated by freeze-drying. This simple

method produced porous **hydrogels**. Irresp. of any rinsing and washing processes, water was homogeneously distributed into the **hydrogel** network, alloying the **hydrogel** network to uniformly enlarge and the ice to act as a porogen during the freezing process. Different porous structures were obtained by varying the freezing temp. **Hydrogels** frozen in liq. nitrogen, had a 2-dimensionally ordered structure, while the **hydrogels** prepd. by freezing temps. near -20.degree., showed a 3-dimensional structure with interconnected pores. As the freezing temp. was lowered, the **hydrogel** structure gradually became more 2-dimensionally ordered. The porosity of dried **hydrogels** can be controlled by the size of ice crystals formed during freezing. The present freeze-drying procedure is a bio-clean method for formulating biodegradable sponges of different pore structures without use of any additives and org. solvents.

L14 ANSWER 16 OF 20 MEDLINE DUPLICATE 10

2001085016 Document Number: 21005450. PubMed ID: 11143369. The effects of crosslinking **density** on cartilage formation in photocrosslinkable **hydrogels**. Bryant S J; Nuttelman C R; Anseth K S. (Department of Chemical Engineering, University of Colorado, Boulder, CO 80309, USA.) BIOMEDICAL SCIENCES INSTRUMENTATION, (1999) 35 309-14. Journal code: 0140524. ISSN: 0067-8856. Pub. country: United States. Language: English.

AB Photoencapsulation of chondrocytes to produce tissue engineered cartilage provides many benefits including rapid polymerization times, the ability to fabricate complex architectures in vivo, and spatial and temporal control during polymerization. Recently, we have examined the cytocompatibility of several photoinitiation schemes and found that low photoinitiator concentrations and light intensities in the ultraviolet and visible range are cytocompatible. In this work, we are currently investigating photocrosslinkable **hydrogels** based on poly(vinyl alcohol) (PVA) and poly(ethylene oxide) (PEO) as scaffolds for **tissue engineering** cartilage. In particular, the influence of the network crosslinking **density**, swelling ratio, and chemical composition on the ability of encapsulated chondrocytes to form extracellular matrix is examined. The cartilage produced in these **hydrogels** will be quantified using biochemical assays that measure DNA content and the amount of sulfated glycosaminoglycans and total collagen in the extracellular matrix. We have demonstrated that chondrocytes encapsulated in a polymer scaffold made from a 20 wt% solution of PEODM/PEO (40 wt% dimethacrylated PEO (MW 3400)/60 wt% PEO (MW 100 K)) form cartilage, and after four weeks the results based on the wet weight of cartilage were approximately 0.03 million cells/mg cartilage, approximately 1.5% glycosaminoglycans and approximately 4.5% total collagen.

L14 ANSWER 17 OF 20 MEDLINE DUPLICATE 11

1999113808 Document Number: 99113808. PubMed ID: 9916770. Alginate **hydrogels** as synthetic extracellular matrix materials. Rowley J A; Madlambayan G; Mooney D J. (Department of Biomedical Engineering, University of Michigan, Colleges of Engineering and Dentistry, Ann Arbor 48109-2136, USA.) BIOMATERIALS, (1999 Jan) 20 (1) 45-53. Journal code: 8100316. ISSN: 0142-9612. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Alginate **hydrogels** are used extensively in cell encapsulation, cell transplantation, and **tissue engineering** applications. Alginates possess many favorable properties required in biomaterials, but are unable to specifically interact with mammalian cells. We have therefore covalently modified alginate polysaccharides with RGD-containing cell adhesion ligands utilizing aqueous carbodiimide chemistry. The chemistry has been optimized and quantified with reaction efficiencies reaching 80% or greater. The concentration of peptide available for reaction was then varied to create **hydrogels** with

a range of ligand **densities**. Mouse skeletal myoblasts were cultured on alginate **hydrogel** surfaces coupled with GRGDY peptides to illustrate achievement of cellular interaction with the otherwise non-adhesive **hydrogel** substrate. Myoblasts adhere to GRGDY-modified alginate surfaces, proliferate, fuse into multinucleated myofibrils, and express heavy-chain myosin which is a differentiation marker for skeletal muscle. Myoblast adhesion and spreading on these GRGDY-modified **hydrogels** was inhibited with soluble ligand added to the seeding medium, illustrating the specificity of adhesion to these materials. Alginate may prove to be an ideal material with which to confer specific cellular interactive properties, potentially allowing for the control of long-term gene expression of cells within these matrices.

L14 ANSWER 18 OF 20 MEDLINE DUPLICATE 12

1998350955 Document Number: 98350955. PubMed ID: 9686338. Role of synthetic extracellular matrix in development of engineered dental pulp. Bohl K S; Shon J; Rutherford B; Mooney D J. (Department of Chemical Engineering, University of Michigan, Ann Arbor 48109, USA.) JOURNAL OF BIOMATERIALS SCIENCE, POLYMER EDITION, (1998) 9 (7) 749-64. Journal code: 9007393. ISSN: 0920-5063. Pub. country: Netherlands. Language: English.

AB In cases of damaged oral tissues, traditional therapies, such as a root canal, replace the injured tissue with a synthetic material. However, while the materials currently used can offer structural replacement of the lost tissue, they are incapable of completely replacing the function of the original tissue, and often fail over time. This report describes a **tissue engineering** approach to dental pulp tissue replacement utilizing cultured cells seeded upon synthetic extracellular matrices. Human pulp fibroblasts were obtained and multiplied in culture. These cells were then seeded onto three different synthetic matrices: scaffolds fabricated from polyglycolic acid (PGA) fibers, a type I collagen **hydrogel**, and alginate in an effort to examine which matrix is most suitable for dental pulp tissue formation. In addition, methods previously developed for seeding and culturing pulp cells on PGA were optimized. Culturing cells on PGA resulted in a very high cell **density** tissue with significant collagen deposition. No cell proliferation was observed on alginate, and the growth of cells in collagen gels after 45 days was only moderate. These studies indicate dental pulp-like tissues can be engineered, and this may provide the first step to engineering a complete tooth.

L14 ANSWER 19 OF 20 MEDLINE DUPLICATE 13

1998261675 Document Number: 98261675. PubMed ID: 9599309. In vitro and in vivo models for the reconstruction of intercellular signaling. Bouhadir K H; Mooney D J. (Department of Chemical Engineering, University of Michigan, Ann Arbor 48109, USA.) ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1998 Apr 15) 842 188-94. Ref: 27. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB A critical need in both **tissue-engineering** applications and basic cell culture studies is the development of synthetic extracellular matrices (ECMs) and experimental systems that reconstitute three-dimensional cell-cell interactions and control tissue formation in vitro and in vivo. We have fabricated synthetic ECMs in the form of fiber-based fabrics, highly porous sponges, and **hydrogels** from biodegradable polymers (e.g., polyglycolic acid) and tested their ability to regulate tissue formation. Both cell seeding onto these synthetic ECMs and subsequent culture conditions can be varied to control initial cell-cell interactions and subsequent cell growth and tissue development. Three-dimensional tissues composed of cells of interest, matrix produced by these cells, and the synthetic ECM (until it degrades) can be created with these systems. For example, smooth muscle cells can be grown on polyglycolic acid fiber-based synthetic ECMs to produce tissues with cell **densities** in excess of 10(8) cells/mL. These tissues contain extensive elastin and collagen, and the smooth muscle cells within

the tissue express the contractile phenotype (e.g., alpha-actin staining). Similar approaches can be used to grow a number of other tissues (e.g., dental pulp) that resemble the native tissue. These engineered tissues may provide novel experimental systems to study the role of three-dimensional intercellular signaling in tissue development and may also find clinical application as replacements to lost or damaged tissues.

L14 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2002 ACS
1999:33148 Document No. 130:200893 Alginate **hydrogels** as synthetic extracellular matrix materials. Rowley, Jon A.; Madlambayan, Gerard; Mooneyb, David J. (Department of Biomedical Engineering, Colleges of Engineering and Dentistrvy, University of Michigan, Ann Arbor, MI, 48109-2136, USA). Biomaterials, Volume Date 1999, 20(1), 45-53 (English) 1998. CODEN: BIMADU. ISSN: 0142-9612. Publisher: Elsevier Science Ltd..
AB Alginate **hydrogels** are used extensively in cell encapsulation, cell transplantation, and **tissue engineering** applications. Alginates have many favorable properties required in biomaterials, but are unable to specifically interact with mammalian cells. We therefore covalently modified alginate polysaccharides with RGD-contg. cell adhesion ligands utilizing aq. carbodiimide chem. The chem. was optimized and quantified with reaction efficiencies reaching 80% or greater. The concn. of peptide available for reaction was then varied to create **hydrogels** with a range of ligand **densities**. Mouse skeletal myoblasts were cultured on alginate **hydrogel** surfaces coupled with GRGDY peptides to illustrate achievement of cellular interaction with the otherwise non-adhesive **hydrogel** substrate. Myoblasts adhere to GRGDY-modified alginate surfaces, proliferate, fuse into multinucleated myofibrils, and express heavy-chain myosin which is a differentiation marker for skeletal muscle. Myoblast adhesion and spreading on these GRGDY-modified **hydrogels** was inhibited with sol. ligand added to the seeding medium, illustrating the specificity of adhesion to these materials. Alginate maybe an ideal material with which to confer specific cellular interactive properties, potentially allowing for the control of long-term gene expression of cells within these matrixes.

=> s l9 and alginate
L15 97 L9 AND ALGINATE

=> s l15 and collagen
L16 31 L15 AND COLLAGEN

=> s l16 and hyaluronic acid
L17 5 L16 AND HYALURONIC ACID

=> s l17 and polyethylene glycol
L18 1 L17 AND POLYETHYLENE GLYCOL

=> d l18 cbib abs

L18 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2001:906235 Document No. 136:25166 Method for composite cell-based implants using mineral or polymeric microcarriers. Frondoza, Carmelita G.; Hungerford, David S.; Shikani, Alan H.; Domb, Abraham J.; Fink, David J.; Bloom, Leonard (Chondros, Inc., USA). U.S. Pat. Appl. Publ. US 20010051834 A1 20011213, 13 pp., Cont.-in-part of U. S. Ser. No. 825,632. (English). CODEN: USXXCO. APPLICATION: US 2001-922909 20010806. PRIORITY: US 1999-275319 19990324; US 2000-712662 20001114; US 2001-825632 20010404.
AB This invention is a method for the implantation of a combination of cells or cell-microcarrier aggregates wherein one component comprises a solid implantable construct and a second component comprises an injectable

formulation. For example, in one embodiment, the solid implant may be first implanted to fill the majority of the cavity receiving the implant, and then cells or cell-microcarrier aggregates in an injectable format, with or without the addn. of gelling materials to promote rapid gelling in situ, may be injected into spaces surrounding the solid implant in order to secure the solid implant in the site and/or to promote rapid adherence and/or integration of the solid implant to surrounding tissues. Also contemplated in this embodiment is that the cellular compn. of the injectable component may differ from that of the solid component. For example, the solid implant may result from the culturing of chondrocytes on microcarriers or scaffolds, e.g., calcium carbonate, calcium phosphate or calcium sulfate, biopolymers, or synthetic polymers such as polylactic acid, polyglycolic or their copolymers, thereby resulting in an implant having cartilage-like properties, whereas the injectable cells or aggregates may result from the culturing of stem cells, resulting thereby in cells capable of producing cells of a chondrogenic, fibroblastic, myoblastic or osteoblastic phenotype. In this example, cells in the injectable aggregates may promote the fixation to or rapid integration of the solid cartilage implant into surrounding cartilage, connective tissue, muscle or bone, resp. A method of treating a skin lesion or nose or ear defects comprises filling the lesion or defect with a solid cell-contg. implant along with an injectable cell-contg. formulation.

=> dup remove l15
PROCESSING COMPLETED FOR L15
L19 54 DUP REMOVE L15 (43 DUPLICATES REMOVED)

=> dup remove l16
PROCESSING COMPLETED FOR L16
L20 17 DUP REMOVE L16 (14 DUPLICATES REMOVED)

=> d l20 1-17 cbib abs

L20 ANSWER 1 OF 17 MEDLINE
2002339362 Document Number: 22076703. PubMed ID: 12081878. Biological response of chondrocytes to **hydrogels**. Elisseeff J H; Lee A; Kleinman H K; Yamada Y. (Whitaker Institute of Biomedical Engineering, Department of Biomedical Engineering, Johns Hopkins University, 3400 N. Charles Street, Baltimore, MD 21218, USA.. jhe@bme.jhu.edu) . ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (2002 Jun) 961 118-22. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.
AB Primary bovine chondrocytes were encapsulated in **alginate** and **alginate** combined with cartilage matrix extract, Cartrigel, for the purpose of cartilage **tissue engineering**. The cell constructs were incubated in vitro and gene expression of cartilage-specific extracellular matrix molecules was quantitated and localized with in situ hybridization with a decrease in expression observed in the **alginate**-Cartrigel constructs. Further understanding of cell response to scaffolds will allow rational design and development of **hydrogels** for cartilage **tissue engineering**.

L20 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2002 ACS
2001:906235 Document No. 136:25166 Method for composite cell-based implants using mineral or polymeric microcarriers. Frondoza, Carmelita G.; Hungerford, David S.; Shikani, Alan H.; Domb, Abraham J.; Fink, David J.; Bloom, Leonard (Chondros, Inc., USA). U.S. Pat. Appl. Publ. US 20010051834 A1 20011213, 13 pp., Cont.-in-part of U. S. Ser. No. 825,632. (English). CODEN: USXXCO. APPLICATION: US 2001-922909 20010806. PRIORITY: US 1999-275319 19990324; US 2000-712662 20001114; US 2001-825632 20010404.
AB This invention is a method for the implantation of a combination of cells

or cell-microcarrier aggregates wherein one component comprises a solid implantable construct and a second component comprises an injectable formulation. For example, in one embodiment, the solid implant may be first implanted to fill the majority of the cavity receiving the implant, and then cells or cell-microcarrier aggregates in an injectable format, with or without the addn. of gelling materials to promote rapid gelling in situ, may be injected into spaces surrounding the solid implant in order to secure the solid implant in the site and/or to promote rapid adherence and/or integration of the solid implant to surrounding tissues. Also contemplated in this embodiment is that the cellular compn. of the injectable component may differ from that of the solid component. For example, the solid implant may result from the culturing of chondrocytes on microcarriers or scaffolds, e.g., calcium carbonate, calcium phosphate or calcium sulfate, biopolymers, or synthetic polymers such as polylactic acid, polyglycolic or their copolymers, thereby resulting in an implant having cartilage-like properties, whereas the injectable cells or aggregates may result from the culturing of stem cells, resulting thereby in cells capable of producing cells of a chondrogenic, fibroblastic, myoblastic or osteoblastic phenotype. In this example, cells in the injectable aggregates may promote the fixation to or rapid integration of the solid cartilage implant into surrounding cartilage, connective tissue, muscle or bone, resp. A method of treating a skin lesion or nose or ear defects comprises filling the lesion or defect with a solid cell-contg. implant along with an injectable cell-contg. formulation.

L20 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2002 ACS
2001:390992 Document No. 135:127003 **Hydrogels** for **Tissue Engineering**. Lee, Kuen Yong; Mooney, David J. (Departments of Biologic & Materials Sciences Chemical Engineering and Biomedical Engineering, University of Michigan, Ann Arbor, MI, 48109, USA). Chemical Reviews (Washington, D. C.), 101(7), 1869-1879 (English) 2001. CODEN: CHREAY. ISSN: 0009-2665. Publisher: American Chemical Society.
AB A review, with 154 refs. Design parameters for **hydrogels** in **tissue engineering**, **hydrogels** from natural polymers (**collagen**, gelatin, hyaluronate, fibrin, **alginate**, agarose, and chitin), **hydrogels** from synthetic polymers (polyacrylic acid and derivs., polyethylene oxide and copolymers, polyvinyl alc., polyphosphazene, and polypeptides), and future perspectives are indexed.

L20 ANSWER 4 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2002:42623 Document No.: PREV200200042623. Growth factor release from **tissue engineering** scaffolds. Whitaker, M. J.; Quirk, R. A.; Howdle, S. M.; Shakesheff, K. M. (1). (1) School of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham, NG7 2RD UK. Journal of Pharmacy and Pharmacology, (November, 2001) Vol. 53, No. 11, pp. 1427-1437. print. ISSN: 0022-3573. Language: English.
AB Synthetic scaffold materials are used in **tissue engineering** for a variety of applications, including physical supports for the creation of functional tissues, protective gels to aid in wound healing and to encapsulate cells for localized hormone-delivery therapies. In order to encourage successful tissue growth, these scaffold materials must incorporate vital growth factors that are released to control their development. A major challenge lies in the requirement for these growth factor delivery mechanisms to mimic the in-vivo release profiles of factors produced during natural tissue morphogenesis or repair. This review highlights some of the major strategies for creating scaffold constructs reported thus far, along with the approaches taken to incorporate growth factors within the materials and the benefits of combining **tissue engineering** and drug delivery expertise.

L20 ANSWER 5 OF 17 MEDLINE DUPLICATE 1

2002004720 Document Number: 21625432. PubMed ID: 11749735. Effect of oxygen tension and **alginate** encapsulation on restoration of the differentiated phenotype of passaged chondrocytes. Murphy C L; Sambanis A. (Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta 30332-0100, USA.) TISSUE ENGINEERING, (2001 Dec) 7 (6) 791-803. Journal code: 9505538. ISSN: 1076-3279. Pub. country: United States. Language: English.

AB The implantation of laboratory-grown tissue offers a valuable alternative approach to the treatment of cartilage defects. Procuring sufficient cell numbers for such tissue-engineered cartilage is a major problem since amplification of chondrocytes in culture typically leads to loss of normal cell phenotype yielding cartilage of inferior quality. In an effort to overcome this problem, we endeavored to regain the differentiated phenotype of chondrocytes after extensive proliferation in monolayer culture by modulating cell morphology and oxygen tension towards the in vivo state. Passaged cells were encapsulated in **alginate hydrogel** in an effort to regain the more rounded shape characteristic of differentiated chondrocytes. These cultures were exposed to reduced (5%-i.e., physiological), or control (20%) oxygen tensions. Both **alginate** encapsulation and reduced oxygen tension significantly upregulated **collagen** II and aggrecan core protein expression (differentiation markers). In fact, after 4 weeks in **alginate** at 5% oxygen, differentiated gene expression was comparable to primary chondrocytes. **Collagen** I expression (dedifferentiation marker) decreased dramatically after **alginate** entrapment, while reduced oxygen tension had no effect. It is concluded that **alginate** encapsulation and reduced oxygen tension help restore key differentiated phenotypic markers of passaged chondrocytes. These findings have important implications for cartilage **tissue engineering**, since they enable the increase in differentiated cell numbers needed for the in vitro development of functional cartilaginous tissue suitable for implantation.

L20 ANSWER 6 OF 17 MEDLINE DUPLICATE 2

2001642039 Document Number: 21551713. PubMed ID: 11694187. A novel use of **alginate hydrogel** as Schwann cell matrix. Mosahebi A; Simon M; Wiberg M; Terenghi G. (Blond McIndoe Centre, University Department of Surgery, Royal Free & University College Medical School, Royal Free Campus, London, United Kingdom.) TISSUE ENGINEERING, (2001 Oct) 7 (5) 525-34. Journal code: 9505538. ISSN: 1076-3279. Pub. country: United States. Language: English.

AB The use of bioresorbable conduits supplemented with Schwann cells (SCs) is a promising **tissue engineering** technique to replace nerve grafting. **Alginate hydrogel** (AH), as a SC **tissue engineering** matrix, has many advantages over previously used matrices but has not been evaluated for this purpose. In this study, the viability and proliferation of SCs together with SC function in AH was evaluated in vitro. AlamarBlue cell assay was used to monitor the viability of SCs in AH and compared to SC viability in **collagen** gel, fibrin glue, hyaluronic acid, Matrigel, and standard culture plate over 5 days in culture. The results showed that the viability and growth of SCs in different matrices over the culture period did not significantly differ to culture plate culture. SC function when suspended in AH was monitored using chick embryo dorsal root ganglia (CDRG) growth assay. Growth of CDRG in AH with or without SCs was compared to CDRG growth without AH matrix. After 3 days in culture, the mean length of neurite sprouting was measured. The results showed that there was neurite growth in AH but was reduced to 43% of control. The neurite growth in AH was, however, enhanced by 170% when SCs were suspended in the gel. In conclusion, AH supported SC viability and function in vitro and may be useful in peripheral nerve **tissue engineering** in reconstructive procedures.

L20 ANSWER 7 OF 17 MEDLINE
2002027936 Document Number: 21376207. PubMed ID: 11484190. Sodium **alginate** sponges with or without sodium hyaluronate: in vitro engineering of cartilage. Miralles G; Baudoin R; Dumas D; Baptiste D; Hubert P; Stoltz J F; Dellacherie E; Mainard D; Netter P; Payan E. (Laboratoire de Physiopathologie et Pharmacologie Articulaires, UMR 7561 CNRS-UHP, Faculte de Medecine, BP 184, 54505, Vandoeuvre les Nancy, France.) JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, (2001 Nov) 57 (2) 268-78. Journal code: 0112726. ISSN: 0021-9304. Pub. country: United States. Language: English.

AB Studies are underway to design biosystems containing embedded chondrocytes to fill osteochondral defects and to produce a tissue close to native cartilage. In the present report, a new **alginate** three-dimensional support for chondrocyte culture is described. A sodium **alginate** solution, with or without hyaluronic acid (HA), was freeze-dried to obtain large-porosity sponges. This formulation was compared with a **hydrogel** of the same composition. In the sponge formulation, macroscopic and microscopic studies demonstrated the formation of a macroporous network (average pore size, 174 microm) associated with a microporous one (average pore size, 250 nm). Histological and biochemical studies showed that, when loaded with HA, the sponge provides an adapted environment for proteoglycan and **collagen** synthesis by chondrocytes. Cytoskeleton organization was studied by three-dimensional fluorescence microscopy (CellScan EPR). Chondrocytes exhibit a marked spherical shape with a nonoriented and sparse actin microfilament network. Type II **collagen** was detected in both types of sponges (with or without HA) using immunohistochemistry. In conclusion, the sponge formulation affords new perspectives with respect to the in vitro production of "artificial" cartilage. Furthermore, the presence of hyaluronate within the **alginate** sponge mimics a functional environment, suitable for the production by embedded chondrocytes of an extracellular matrix. Copyright 2001 John Wiley & Sons, Inc.

L20 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2002 ACS
2001:755406 Document No. 137:83565 Noninvasive detachment of cells on cells. Hara, Masayuki; Yamaki, Ayako; Miyake, Jun (Tissue Engineering Research Center (TERC), National Institute of Advanced Industrial Science and Technology (AIST), Ikeda, Osaka, 563-8577, Japan). Materials Science & Engineering, C: Biomimetic and Supramolecular Systems, C17(1-2), 107-112 (English) 2001. CODEN: MSCEEE. ISSN: 0928-4931. Publisher: Elsevier Science B.V..

AB A novel method was developed to detach a monolayer of cultured cells with a supporting **collagen** gel layer from a calcium **alginate** gel on a porous membrane in a culture dish by treatment with EDTA as a relatively noninvasive method without using protease. This method depends on the principle that **hydrogel** composed of calcium **alginate** is reversibly formed and dissolved in the presence and absence of calcium ions, resp. Three layers of cultured IEC 6 cells and BALB/3T3 cells were laminated with spacer of **collagen** gel layers by this method. The laminated cells remained viable in a normal shape after a 3-day culture.

L20 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2002 ACS
2001:585025 Document No. 135:293905 Synthesis and biological response of novel composite **hydrogels** based on **alginate** and cartilage extracellular matrix (cartrigel). Elisseeff, Jennifer H.; Kleinman, Hynda K.; Yamada, Yoshihiko (Craniofacial Development Biology and Regeneration Branch, National Institute of Dental and Craniofacial Research, Bethesda, MD, 20892, USA). Polymeric Materials Science and Engineering, 85, 49-50 (English) 2001. CODEN: PMSEDG. ISSN: 0743-0515. Publisher: American Chemical Society.

AB Composite **hydrogels** based on **alginate** and cartilage

extracellular matrix (cartrigel) were developed for cartilage **tissue engineering**. Incorporation of natural polymers to form a **hydrogel** composite, as demonstrated in this study, introduced biol. activity creating a **tissue engineering** scaffold with desired phys. and biol. properties, such as swelling and expression of type II **collagen** and aggrecan, two major constituents of cartilage.

L20 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2002 ACS
2001:641526 Synthesis and biological response of novel composite **hydrogels** based on **alginate** and cartilage extracellular matrix (cartrigel). Elisseeff, Jennifer H.; Kleinman, Hynda K.; Yamada, Yoshihiko (Craniofacial Developmental Biology and Regeneration Branch, National Institute of Dental and Craniofacial Research, Bethesda, MD, 20892, USA). Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001, PMSE-030. American Chemical Society: Washington, D. C. (English) 2001. CODEN: 69BUZP.
AB A composite **hydrogel** system based on ionically crosslinking **alginate** and a thermoresponsive ext. from cartilage extracellular matrix (cartrigel) was investigated for use in cartilage **tissue engineering**. Incorporation of cartrigel into **alginate** increased pore size as demonstrated by an increase in the equil. swelling vol. and by Safranin O stained histol. sections. MRNA levels of type II **collagen** and aggrecan decreased after encapsulation in the **hydrogels** but were still higher than native cartilage. Aggrecan expression and deposition was enriched in the periphery of the **alginate** gels yet was more uniform in the composite gels whereas type II **collagen** was evenly distributed throughout both gels. Development of composite **hydrogels** provides the flexibility and control of polymer properties such as porosity or mode of polymn. in the synthetic component with control of biol. properties in the natural component.

L20 ANSWER 11 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2000:288137 Document No.: PREV200000288137. The importance of drug delivery systems in **tissue engineering**. Tabata, Yasuhiko (1). (1) Institute for Frontier Medical Sciences, Kyoto University, 53 Kawara-cho Shogoin Sakyo-ku, Kyoto, 606-8507 Japan. Pharmaceutical Science & Technology Today, (March, 2000) Vol. 3, No. 3, pp. 80-89. print. ISSN: 1461-5347. Language: English. Summary Language: English.
AB **Tissue engineering** is designed to regenerate natural tissues or to create biological substitutes for defective or lost tissues and organs through the use of cells. In addition to cells and their scaffolds, growth factors are required to promote tissue regeneration. Indeed, growth factor-induced vascularization is effective in supplying the oxygen and nutrients necessary for the survival of transplanted cells in organ substitution. However, growth factors have poor in vivo stability and so the biological effects are often unpredictable unless the delivery system is contrived. This review provides several examples to emphasize the importance of drug delivery systems in **tissue engineering**.

L20 ANSWER 12 OF 17 MEDLINE DUPLICATE 3
1999326588 Document Number: 99326588. PubMed ID: 10397930. Bioengineering of elastic cartilage with aggregated porcine and human auricular chondrocytes and **hydrogels** containing **alginate**, **collagen**, and kappa-elastin. de Chalain T; Phillips J H; Hinek A. (Division of Plastic Surgery, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.) JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, (1999 Mar 5) 44 (3) 280-8. Journal code: 0112726. ISSN: 0021-9304. Pub. country: United States. Language: English.
AB Transplantation of isolated chondrocytes has long been acknowledged as a potential method for rebuilding small defects in damaged or deformed

cartilages. Recent advances in **tissue engineering** permit us to focus on production of larger amounts of cartilaginous tissue, such as might be needed for reconstructive surgery of the entire auricle. In this report we describe modification of the basic techniques that lead to production of a large amount of elastic cartilage originated from porcine and human isolated chondrocytes. Small fragments of auricular cartilage were harvested from children undergoing ear reconstruction for microtia or extirpation of preauricular tags and from ears of juvenile pigs. Enzymatically isolated elastic chondrocytes were then agitated in suspension to form the chondronlike aggregates, which were further embedded in molded **hydrogel** constructs made of **alginate** and type I **collagen** augmented with kappa-elastin. The constructs were then implanted in nude mice and harvested 4 and 12 weeks after heterotransplantation. The resulting neocartilage closely resembled native auricular cartilage at the gross, microscopic, and ultrastructural levels. Immunohistochemistry and electron microscopy additionally confirmed that the newly produced cartilage contained the major components of the elastic cartilage-specific matrix, including **collagen** type II, proteoglycans, and well-assembled elastic fibers.

L20 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2002 ACS
1998:197533 Document No. 128:258671 Materials containing polysaccharide chains, particularly **alginates** or modified **alginate** chains. Mooney, David J.; Bouhadir, Kamal H.; Wong, Wai Hung; Rowley, Jon A. (Regents of the University of Michigan, USA; Mooney, David J.; Bouhadir, Kamal H.; Wong, Wai Hung; Rowley, Jon A.). PCT Int. Appl. WO 9812228 A1 19980326, 97 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US16890 19970919. PRIORITY: US 1996-26362 19960919; US 1996-26467 19960919; US 1997-41565 19970321.

AB The title materials comprise polysaccharide chains which may be included as side chains or auxiliary chains from a backbone polymer chain, which may also be a polysaccharide. The polysaccharide, e.g., **alginate** chains may be crosslinked between side chains, auxiliary chains and/or backbone chains. These materials and nonmodified **alginate** materials are advantageously modified by covalent bonding of a biol. active mol. for cell adhesion or other cellular interaction. Processes for prepn. of these **alginate** materials and methods for using them, particularly as polymeric matrixes, e.g., for cell transplantation and **tissue engineering** applications are also claimed.

L20 ANSWER 14 OF 17 MEDLINE DUPLICATE 4
1998350955 Document Number: 98350955. PubMed ID: 9686338. Role of synthetic extracellular matrix in development of engineered dental pulp. Bohl K S; Shon J; Rutherford B; Mooney D J. (Department of Chemical Engineering, University of Michigan, Ann Arbor 48109, USA.) JOURNAL OF BIOMATERIALS SCIENCE, POLYMER EDITION, (1998) 9 (7) 749-64. Journal code: 9007393. ISSN: 0920-5063. Pub. country: Netherlands. Language: English.

AB In cases of damaged oral tissues, traditional therapies, such as a root canal, replace the injured tissue with a synthetic material. However, while the materials currently used can offer structural replacement of the lost tissue, they are incapable of completely replacing the function of the original tissue, and often fail over time. This report describes a **tissue engineering** approach to dental pulp tissue replacement utilizing cultured cells seeded upon synthetic extracellular matrices. Human pulp fibroblasts were obtained and multiplied in culture.

These cells were then seeded onto three different synthetic matrices: scaffolds fabricated from polyglycolic acid (PGA) fibers, a type I **collagen hydrogel**, and **alginate** in an effort to examine which matrix is most suitable for dental pulp tissue formation. In addition, methods previously developed for seeding and culturing pulp cells on PGA were optimized. Culturing cells on PGA resulted in a very high cell density tissue with significant **collagen** deposition. No cell proliferation was observed on **alginate**, and the growth of cells in **collagen** gels after 45 days was only moderate. These studies indicate dental pulp-like tissues can be engineered, and this may provide the first step to engineering a complete tooth.

L20 ANSWER 15 OF 17 MEDLINE DUPLICATE 5

1998311834 Document Number: 98311834. PubMed ID: 9648028. Comparative study of the use of poly(glycolic acid), calcium **alginate** and pluronics in the engineering of autologous porcine cartilage. Cao Y; Rodriguez A; Vacanti M; Ibarra C; Arevalo C; Vacanti C A. (Department of Anesthesia, University of Massachusetts Medical Center, Worcester 01655, USA.) JOURNAL OF BIOMATERIALS SCIENCE, POLYMER EDITION, (1998) 9 (5) 475-87. Journal code: 9007393. ISSN: 0920-5063. Pub. country: Netherlands. Language: English.

AB New cartilage formation has been successfully achieved by technology referred to as **tissue engineering**. Polymers and **hydrogels** such as poly(glycolic acid), calcium **alginate**, and poly(ethylene) and poly(propylene) **hydrogels** have been used as cell carriers to regenerate cartilage in the nude mouse model. The next step toward human applications of engineered cartilage is to demonstrate their potential in immunocompetent animal models. This study compared the suitability of three polymers for generating tissue engineered elastic cartilage using autologous cells in an immuno-competent porcine animal model. Auricular cartilage was obtained from pigs. Chondrocytes were isolated onto fiber based poly(glycolic acid) (PGA) scaffolds or suspended in calcium **alginate** or pluronic F127 gel at constant concentrations. Chondrocyte-polymer constructs were either implanted (PGA) or injected (calcium **alginate** and pluronic) as autologous implants subcutaneously into the pigs from which the cells had been isolated. Specimens were harvested and analyzed grossly and historically after 6 weeks in vivo. All explants demonstrated cartilage formation to a variable degree. When using PGA or calcium **alginate**, the overall histological appearance of the tissue formed is that of fibrocartilage with thick bundles of **collagen** dispersed in the tissue. When using pluronics as scaffold, histologic features resemble those of native elastic cartilage, showing a more organized arrangement of the cells, which seems to correlate to functional properties as elastin presence in the tissue engineered cartilage. Elastic cartilage engineered in an immunocompetent animal model varies with the type of polymer used. The behavior of the cell-polymer constructs is not fully understood and outcome seems to be related to several factors, including inflammatory reaction. Further studies with similar models are needed to determine the feasibility of engineering tissue generated from different cell-polymer constructs prior to human application.

L20 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2002 ACS

1999:538728 Document No. 132:112990 Comparative study of the use of poly(glycolic acid), calcium **alginate** and pluronics in the engineering of autologous porcine cartilage. Cao, Yilin; Rodriguez, Angela; Vacanti, Martin; Ibarra, Clemente; Arevalo, Carlos; Vacanti, Charles A. (Department of Anesthesia, the Laboratory for Tissue Engineering, University of Massachusetts Medical Center, Worcester, MA, 01655, USA). Polymers for Tissue Engineering, 315-327. Editor(s): Shoichet, Molly S.; Hubbell, Jeffrey A. VSP: Utrecht, Neth. (English) 1998. CODEN: 68AEA8.

AB New cartilage formation has been successfully achieved by a technol.

referred to as **tissue engineering**. Polymers and **hydrogels** such as poly(glycolic acid), calcium **alginate**, and poly(ethylene) and Pluronic **hydrogels** have been used as cell carriers to regenerate cartilage in the nude mouse model. The next step toward human applications of engineered cartilage is to demonstrate their potential in immunocompetent animal models. This study compared the suitability of 3 polymers for generating tissue engineered elastic cartilage using autologous cells in an immuno-competent porcine animal model. Auricular cartilage was obtained from pigs. Chondrocytes were isolated and seeded onto fiber based poly(glycolic acid) (PGA) scaffolds or suspended in calcium **alginate** or Pluronic F127 gel at const. concns. Chondrocyte-polymer constructs were either implanted (PGA) or injected (calcium **alginate** and Pluronic) as autologous implants s.c. into the pigs from which the cells had been isolated. Specimens were harvested and analyzed grossly and histol. after 6 wk in vivo. All explants demonstrated cartilage formation to a variable degree. When using PGA or calcium **alginate**, the overall histol. appearance of the tissue formed is that of fibro-cartilage with thick bundles of **collagen** dispersed in the tissue. When using Pluronic as a scaffold, histol. features resemble those of native elastic cartilage, showing a more organized arrangement of the cells, which seems to correlate to functional properties as elastin presence in the tissue engineered cartilage. Elastic cartilage engineered in an immunocompetent animal model varies with the type of the polymer used. The behavior of the cell-polymer constructs is not fully understood and outcome seems to be related to several factors, including inflammatory reaction. Further studies with similar models are needed to det. the feasibility of engineering tissue generated from different cell-polymer constructs prior to human application.

L20 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2002 ACS
1999:538727 Document No. 132:113045 Role of synthetic extracellular matrix in development of engineered dental pulp. Bohl, Kristyn S.; Shon, John; Rutherford, Bruce; Mooney, David J. (Department of Chemical Engineering, University of Michigan, Ann Arbor, MI, 48109, USA). Polymers for Tissue Engineering, 299-314. Editor(s): Shoichet, Molly S.; Hubbell, Jeffrey A. VSP: Utrecht, Neth. (English) 1998. CODEN: 68AEA8.

AB In cases of damaged oral tissues, traditional therapies, such as a root canal, replace the injured tissue with a synthetic material. However, while the materials currently used can offer structural replacement of the lost tissue, they are incapable of completely replacing the function of the original tissue, and often fail over time. This report describes a **tissue engineering** approach to dental pulp tissue replacement utilizing cultured cells seeded upon synthetic extracellular matrixes. Human pulp fibroblasts were obtained and multiplied in culture. These cells were then seeded onto three different synthetic matrixes: scaffolds fabricated from polyglycolic acid (PGA) fibers, a type I **collagen hydrogel**, and **alginate** in an effort to examine which matrix is most suitable for dental pulp tissue formation. In addn., methods previously developed for seeding and culturing pulp cells on PGA were optimized. Culturing cells on PGA resulted in a very high cell d. tissue with significant **collagen** deposition. No cell proliferation was obsd. on **alginate**, and the growth of cells in **collagen** gels after 45 days was only moderate. These studies indicate dental pulp-like tissues can be engineered, and this may provide the first step to engineering a complete tooth.

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L21 3 DUP REMOVE L17 (2 DUPLICATES REMOVED)

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L21 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS
2001:906235 Document No. 136:25166 Method for composite cell-based implants using mineral or polymeric microcarriers. Frondoza, Carmelita G.; Hungerford, David S.; Shikani, Alan H.; Domb, Abraham J.; Fink, David J.; Bloom, Leonard (Chondros, Inc., USA). U.S. Pat. Appl. Publ. US 20010051834 A1 20011213, 13 pp., Cont.-in-part of U. S. Ser. No. 825,632. (English). CODEN: USXXCO. APPLICATION: US 2001-922909 20010806. PRIORITY: US 1999-275319 19990324; US 2000-712662 20001114; US 2001-825632 20010404.

AB This invention is a method for the implantation of a combination of cells or cell-microcarrier aggregates wherein one component comprises a solid implantable construct and a second component comprises an injectable formulation. For example, in one embodiment, the solid implant may be first implanted to fill the majority of the cavity receiving the implant, and then cells or cell-microcarrier aggregates in an injectable format, with or without the addn. of gelling materials to promote rapid gelling in situ, may be injected into spaces surrounding the solid implant in order to secure the solid implant in the site and/or to promote rapid adherence and/or integration of the solid implant to surrounding tissues. Also contemplated in this embodiment is that the cellular compn. of the injectable component may differ from that of the solid component. For example, the solid implant may result from the culturing of chondrocytes on microcarriers or scaffolds, e.g., calcium carbonate, calcium phosphate or calcium sulfate, biopolymers, or synthetic polymers such as polylactic acid, polyglycolic or their copolymers, thereby resulting in an implant having cartilage-like properties, whereas the injectable cells or aggregates may result from the culturing of stem cells, resulting thereby in cells capable of producing cells of a chondrogenic, fibroblastic, myoblastic or osteoblastic phenotype. In this example, cells in the injectable aggregates may promote the fixation to or rapid integration of the solid cartilage implant into surrounding cartilage, connective tissue, muscle or bone, resp. A method of treating a skin lesion or nose or ear defects comprises filling the lesion or defect with a solid cell-contg. implant along with an injectable cell-contg. formulation.

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L24 10 DUP REMOVE L23 (20 DUPLICATES REMOVED)

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L24 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2002 ACS
2002:157948 Document No. 136:205503 **Tissue engineering** scaffolds promoting matrix protein production. **West, Jennifer L.** ; **Mann, Brenda K.** (Rice University, USA). PCT Int. Appl. WO 2002016557 A2 20020228, 25 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US26170 20010821. PRIORITY: US 2000-PV226771 20000821.

AB Matrix-enhancing mols., such as TGF-.beta., are conjugated to or immobilized on scaffolds to increase ECM prodn. by cells for **tissue engineering**, tissue regeneration and wound healing applications. The matrix-enhancing mol. is conjugated to a tether, such as polyethylene glycol (PEG) monoacrylate, for attachment to a **tissue engineering** or cell growth scaffold. The matrix-enhancing mol. retains activity after attachment to the scaffold, and causes cells growing in or on the scaffold to increase extracellular matrix (ECM) prodn., without substantially increasing proliferation of the cells, even when the scaffold addnl. contains cell adhesion ligands. The increased ECM produced by the cells aids in maintaining the integrity of the scaffold, particularly when the scaffold is degradable, either by hydrolysis or by enzymic degrdn. For example, TNF.beta. was conjugated to polyethylene glycol by reacting TNF.beta. with acryloyl-PEG-N-hydroxysuccinimide in TRIS buffer (pH 8.5) for 2 h. The mixt. was then lyophilized and stored frozen. Smooth muscle cells were cultured in presence of 0.04 pmol/mL acryloyl-PEG-TGF.beta. and prodn. of extracellular matrix protein was evaluated.

L24 ANSWER 2 OF 10 MEDLINE DUPLICATE 1
2002461311 Document Number: 22208130. PubMed ID: 12219822.
Photocrosslinkable polyvinyl alcohol hydrogels that can be modified with cell adhesion peptides for use in **tissue engineering**.
Schmedlen Rachael H; Masters Kristyn S; **West Jennifer L.**
(Department of Bioengineering, Rice University, Houston, TX 77005-1892, USA.) BIOMATERIALS, (2002 Nov) 23 (22) 4325-32. Journal code: 8100316. ISSN: 0142-9612. Pub. country: England: United Kingdom. Language: English.
AB Photoactive polyvinyl alcohol hydrogels (PVA) have been investigated for use as **tissue engineering** scaffolds. These materials allow in situ polymerization for minimally invasive implantation methods. The mechanical properties of these materials can be tailored for a variety of soft tissue applications. The Young's modulus and ultimate tensile strength of PVA hydrogels are increased with increasing polymer concentration, and highly elastic hydrogels can be formed by altering the number of crosslinkable groups per chain. Fibroblasts homogeneously seeded within 3 mm thick PVA hydrogels remained viable throughout 2 weeks in culture, with no differences in viability across the thickness of the hydrogel. Cells seeded within the PVA hydrogels also produce extracellular matrix proteins, as indicated by the production of hydroxyproline during culture. Intrinsically cell non-adhesive, these PVA hydrogels were functionalized with the cell-adhesive peptide RGDS and found to support the attachment and spreading of fibroblasts in a dose-dependent manner. These results suggest that photopolymerizable PVA hydrogels are promising for **tissue engineering** applications.

L24 ANSWER 3 OF 10 MEDLINE DUPLICATE 2
2002461309 Document Number: 22208128. PubMed ID: 12219820.
Photopolymerizable hydrogels for **tissue engineering** applications. Nguyen Kytai Truong; **West Jennifer L.** (Department of Bioengineering, Rice University, Houston, TX 77251-1892, USA.) BIOMATERIALS, (2002 Nov) 23 (22) 4307-14. Journal code: 8100316. ISSN: 0142-9612. Pub. country: England: United Kingdom. Language: English.
AB Photopolymerized hydrogels are being investigated for a number of **tissue engineering** applications because of the ability to form these materials in situ in a minimally invasive manner such as by injection. In addition, hydrogels, three-dimensional networks of hydrophilic polymers that are able to swell large amounts of water, can be made to resemble the physical characteristics of soft tissues. Hydrogel materials also generally exhibit high permeability and good biocompatibility making, these materials attractive for use in cell encapsulation and **tissue engineering** applications. A number of hydrogel materials can be formed via photopolymerization processes mild enough to be carried out in the presence of living cells.

This allows one to homogeneously seed cells throughout the scaffold material and to form hydrogels in situ. This review presents advantages of photopolymerization of hydrogels and describes the photoinitiators and materials in current use. Applications of photopolymerized hydrogels in **tissue engineering** that have been investigated are summarized.

L24 ANSWER 4 OF 10 MEDLINE DUPLICATE 3
2002103796 Document Number: 21823893. PubMed ID: 11835163. Cell adhesion peptides alter smooth muscle cell adhesion, proliferation, migration, and matrix protein synthesis on modified surfaces and in polymer scaffolds. **Mann Brenda K; West Jennifer L.** (Rice University, Department of Bioengineering, P.O. Box 1892, MS-142, Houston, Texas 77251-1892, USA.) JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, (2002 Apr) 60 (1) 86-93. Journal code: 0112726. ISSN: 0021-9304. Pub. country: United States. Language: English.

AB The effects of cell adhesion peptides (RGDS, KQAGDV, VAPG) on vascular smooth muscle cells grown on modified surfaces and in **tissue-engineering** scaffolds were examined. Cells were more strongly adhered to surfaces modified with adhesive ligands than to control surfaces (no ligand or a nonadhesive ligand). Cell migration was higher on surfaces with 0.2 nmol/cm(2) of adhesive ligand than on control surfaces, but it was lower on surfaces with 2.0 nmol/cm(2) of adhesive ligand than it was on control surfaces. Further, cell proliferation was lower on adhesive surfaces than it was on control surfaces, and it decreased as the ligand density increased. Similarly, in the peptide-grafted hydrogel scaffolds, cell proliferation was lower in scaffolds containing the adhesive peptides than it was in control scaffolds. After 7 days of culture, more collagen per cell was produced in control scaffolds than in scaffolds containing adhesive peptides. In addition, collagen production decreased in the scaffolds as the ligand concentration increased. While modification of a surface or scaffold material with adhesive ligands initially increases cell attachment, it may be necessary to optimize cell adhesion simultaneously with proliferation, migration, and matrix production.

L24 ANSWER 5 OF 10 MEDLINE DUPLICATE 4
2001529723 Document Number: 21459300. PubMed ID: 11575479. Smooth muscle cell growth in photopolymerized hydrogels with cell adhesive and proteolytically degradable domains: synthetic ECM analogs for **tissue engineering**. **Mann B K**; Gobin A S; Tsai A T; Schmedlen R H; **West J L.** (Department of Bioengineering, Rice University, Houston, TX 77005-1892, USA.) BIOMATERIALS, (2001 Nov) 22 (22) 3045-51. Journal code: 8100316. ISSN: 0142-9612. Pub. country: England: United Kingdom. Language: English.

AB Photopolymerizable polyethylene glycol (PEG) derivatives have been investigated as hydrogel **tissue engineering** scaffolds. These materials have been modified with bioactive peptides in order to create materials that mimic some of the properties of the natural extracellular matrix (ECM). The PEG derivatives with proteolytically degradable peptides in their backbone have been used to form hydrogels that are degraded by enzymes involved in cell migration, such as collagenase and elastase. Cell adhesive peptides, such as the peptide RGD, have been grafted into photopolymerized hydrogels to achieve biospecific cell adhesion. Cells seeded homogeneously in the hydrogels during photopolymerization remain viable, proliferate, and produce ECM proteins. Cells can also migrate through hydrogels that contain both proteolytically degradable and cell adhesive peptides. The biological activities of these materials can be tailored to meet the requirements of a given **tissue engineering** application by creating a mixture of various bioactive PEG derivatives prior to photopolymerization.

L24 ANSWER 6 OF 10 MEDLINE DUPLICATE 5
2001180447 Document Number: 21082691. PubMed ID: 11214754.
Tethered-TGF-beta increases extracellular matrix production of vascular smooth muscle cells. **Mann B K**; Schmedlen R H; **West J L**. (Department of Bioengineering, Rice University, Houston, TX 77251-1892, USA.) BIOMATERIALS, (2001 Mar) 22 (5) 439-44. Journal code: 8100316. ISSN: 0142-9612. Pub. country: England: United Kingdom. Language: English.

AB Biomaterials developed for **tissue engineering** and wound healing applications need to support robust cell adhesion, yet also need to be replaced by new tissue synthesized by those cells. In order to maintain mechanical integrity of the tissue, the cells must generate sufficient extracellular matrix before the scaffold is degraded. We have previously shown that materials containing cell adhesive ligands to promote or improve cell adhesion can decrease extracellular matrix production (Mann et al., Modification of surfaces with cell adhesion peptides alters extracellular matrix deposition. Biomaterials 1999;20:2281-6). Such decreased matrix production by cells in **tissue engineering** scaffolds may result in tissue failure. However, we have found that TGF-beta1 can be used in scaffolds to dramatically increase matrix production. Matrix production by vascular smooth muscle cells grown on adhesive ligand-modified glass surfaces and in PEG hydrogels containing covalently bound adhesive ligands was increased in the presence of 0.04 pmol/ml (1 ng/ml) TGF-beta1. TGF-beta1 can counteract the effect of these adhesive ligands on matrix production; matrix production could be increased even above that observed in the absence of adhesive peptides. Further, TGF-beta1 covalently immobilized to PEG retained its ability to increase matrix production. Tethering TGF-beta1 to the polymer scaffold resulted in a significant increase in matrix production over the same amount of soluble TGF-beta1.

L24 ANSWER 7 OF 10 MEDLINE DUPLICATE 6
2001454387 Document Number: 21391550. PubMed ID: 11500813. **Tissue engineering** in the cardiovascular system: progress toward a tissue engineered heart. **Mann B K; West J L.** (Rice University, Department of Bioengineering, Houston, Texas 77251-1892, USA.) ANATOMICAL RECORD, (2001 Aug 1) 263 (4) 367-71. Ref: 42. Journal code: 0370540. ISSN: 0003-276X. Pub. country: United States. Language: English.

AB Achieving the lofty goal of developing a tissue engineered heart will likely rely on progress in engineering the various components: blood vessels, heart valves, and cardiac muscle. Advances in tissue engineered vascular grafts have shown the most progress to date. Research in tissue-engineered vascular grafts has focused on improving scaffold design, including mechanical properties and bioactivity; genetically engineering cells to improve graft performance; and optimizing tissue formation through in vitro mechanical conditioning. Some of these same approaches have been used in developing **tissue engineering** heart valves and cardiac muscle as well. Continued advances in scaffold technology and a greater understanding of vascular cell biology along with collaboration among engineers, scientists, and physicians will lead to further progress in the field of cardiovascular **tissue engineering** and ultimately the development of a tissue-engineered heart.

L24 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2002 ACS
2001:639795 Synthetic ECM analogs: Biofunctional polymers for **tissue engineering**. **West, Jennifer L.** (Bioengineering, Rice University, Houston, TX, 77005, USA). Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001, MACR-007. American Chemical Society: Washington, D. C. (English) 2001. CODEN: 69BUZP.

AB Synthetic hydrogel materials have been developed that mimic many of the properties of the extracellular matrix (ECM). These materials are

degraded by the proteolytic enzymes involved in cell migration and tissue remodeling, interact with cell surface receptors to mediate cell adhesion and focal contact formation, and contain tethered growth factors in order to manipulate cell behavior to optimize tissue formation. These materials are acrylated copolymers of polyethylene glycol and bioactive peptides and/or polysaccharides. Cells can be mixed with aq. polymer solns. When this mixt. is photocrosslinked, the cells are homogeneously seeded throughout the hydrogel scaffold. The mech. properties of the scaffold can be manipulated to match many soft tissues. Cells have been cultured in these scaffolds within pulsatile flow bioreactors to form tissue engineered vascular grafts.

L24 ANSWER 9 OF 10 MEDLINE DUPLICATE 7

2000080597 Document Number: 20080597. PubMed ID: 10614934. Modification of surfaces with cell adhesion peptides alters extracellular matrix deposition. **Mann B K**; Tsai A T; Scott-Burden T; **West J L** . (Department of Bioengineering, Rice University, Houston, TX 77285-1892, USA.) BIOMATERIALS, (1999 Dec) 20 (23-24) 2281-6. Journal code: 8100316. ISSN: 0142-9612. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The goal of the current study was to evaluate matrix protein synthesis by cells cultured on materials that had been modified with cell adhesion ligands. We examined the effects of surface peptide density and of peptides with different affinities on the extracellular matrix production of smooth muscle cells, endothelial cells and fibroblasts. While initial adhesion was greatest on the higher density peptide surfaces, all cell types exhibited decreased matrix production on the more highly adhesive surfaces. Similarly, when different peptides were evaluated, matrix production was the lowest on the most adhesive surface and highest on the least adhesive surface. These results suggest that extracellular matrix synthesis may be regulated, to some extent, by signal transduction initiated by adhesion events. This may pose limitations for use of bioactive materials as **tissue engineering** scaffolds, as matrix production is an important aspect of tissue formation. However, it may be possible to increase matrix production on highly adhesive surfaces using exogenous factors. TGF-beta was shown to increase matrix production by both smooth muscle cells and endothelial cells.

L24 ANSWER 10 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

1997:368638 Document No.: PREV199799667841. Bioactive polymers. **West, Jennifer L. (1)**; Hubbell, Jeffrey A.. (1) Dep. Bioeng., Rice Univ., Houston, TX 77251-1892 USA. Atala, A. [Editor]; Mooney, D. J. [Editor]. (1997) pp. 83-95. Tissue Engineering; Synthetic biodegradable polymer scaffolds. Publisher: Birkhaeuser Boston, Inc. 675 Massachusetts Avenue, Cambridge, Massachusetts 02139, USA. ISBN: 0-8176-3919-5, 3-7643-3919-5. Language: English.